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Slug, CD44 and Her-2/neu Immunohistochemical Expression in Gastric Carcinoma

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Abstract

Background: The major prognostic factors in carcinoma of the stomach are the depth of invasion into the gastric wall and the degree of differentiation of the tumor. However, there is no reliable parameter predicting the risk of recurrence or progression. Molecular markers are, therefore, required to estimate the individual prognosis of patients as well as for effective treatment.

Aim of Study: To evaluate the immunohistochemical expression of Sulg, CD44 and Her-2/neu in gastric carcinoma and to correlate slug and CD44 expression as prognostic markers with available clinicopathologic features, correlate Her-2/neu as predictive marker with clinicopathologic features and to correlate the relation between slug, CD44 and Her-2/neu expressions.

Material and Methods: Slug, CD44 and Her-2/Neu were assessed by immunohistochemistry in 50 specimens of gastric carcinoma, collected from Al-Azhar Faculty of Medicine Hospital labs and some private labs, within the period from November 2017 to February 2021. All specimens were obtained through gastrectomy.

Results: There were statistically significant relations between Slug and CD44 immunohistochemical expressions in gastric carcinomas, and distal tumor locations, high pT stage and high pN stage. And there was significantly relation between Her-2/neu expression and proximal tumor location, histopathological type/grade and advanced pT stage.

Conclusion: Slug, CD44 and Her-2 / neuimmunohistochemical expressions were directly related to stage of gastric carcinomas and could be of valuable significance in predicting the aggressive invasive gastric tumors and subsequently the need to aggressive treatment options.

Key Words: *Immunohistochemical expression of Slug – CD44 – Her-2/neu – Gastric carcinoma.*

Introduction

ONCE the second most common cancer worldwide, stomach cancer has dropped to sixth place, after cancers of the lung, breast, prostate, colon/rectum, and skin (non-melanoma). Stomach cancer is the third most common cause of death from cancer [1]. In Egypt, according to the National Cancer Institute registry, it represents 1.64% of all cancers in Egypt and 14.72% of digestive system malignant tumorswith median age of 55 years and male predominance [2]. The high mortality rate from gastric cancer (GC) is mainly related to latediagnosis and to the lack of programs for early detection of this tumor. Thus,novel treatment options and predictors of treatment response are needed [3]. Gastric cancer has one of the most complex genetic pathways with lots of questions still remained to be clarified. There are currently no definitive geneticmarkers for gastric cancer risk stratification that can be applied to all populations. More importantly, translating this genomic datainto more effective treatments for gastric cancer remains the major challenge [4]. Recent investigations have revealed that cancer cell activation of EMT (Epithelial-mesenchymal transition) contributes to cell invasion and metastasis in multiple cancers including gastric cancer [5]. Epithelial-mesenchymal transition (EMT) is a biologic process by which epithelial cells lose their cell-cell junctions and apical-basal polarity and gain a highly motile and invasive phenotype to become mesenchymal cells [6]. As already reported in many studies, the switch in EMT process is performed by transcription factors, including the Snail family members Snail1 (Snail) and Snail2 (also addressed as Slug) [7]. In some studies, high Slug expression was correlated with advanced stages and worse clinical outcomes [8]. EMT has been confirmed to play a critical role in tumor metastasis and recurrence, which have been shown to be tightly linked with the function of CSCs [9]. As CD44 family proteins can mediate Epithelial-mesenchymal transition [10,11]. Additionally, reports have demonstrated that cells undergo-

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ing EMT can acquire stem cell-like characteristics, which indicated an interesting conjunction between EMT and stem cells [12,13]. Accumulating evidences indicate that there is a link between CSCs and EMT in gastric cancer. EMT could provide a new perspective for CSCs theory [14]. Human epidermal growth factor receptor 2 (Her-2/ERBB2/neu), a member of the epidermal growth factor receptor family of receptor tyrosine kinases, is over expressed in 7%-34% of GC cases [15]. Her-2 could promote the invasion and migration of gastric cancer cells through EMT [16]. Up to date, trastuzumab is the only target approved as the first-line treatment of Her-2 positive metastatic gastric cancer [17]. So, investigating for Her-2 positivity is beneficial for treatment planning. Owing to existence of a variety of distinct histomorphological tumor typeswhich differ in prognosis, gastric carcinoma appears to be an appropriate tumorto investigate the correlation between (EMT) and Hre2/neu expression andclinical behavior including aggressiveness of the tumor and metastasis [18].

Material and Methods

This work included 50 specimens of gastric carcinoma, collected from Al-Azhar Faculty of Medicine Hospital labs and some private labs during the period from November 2017 to February 2021. Specimens were obtained by gastrectomy. All the specimens were formalin fixed, and paraffin embedded. For all specimens, clinical data were available including clinical history and sex and age of the patients. Four micron thick sections were cut from paraffin blocks of all cases and stained with hematoxylin and eosin (H&E) for histological re-evaluation. All cases were re-evaluated; graded and staged according to the classification of WHO 2019 and TNM staging system respectively [19].

For immunohistochemical study; unstained positively charged slides were prepared from each paraffin block for immunostaining with mouse monoclonal antibodies against: Slug and CD44 and rabbit monoclonal antibodies against Her-2/neu. Immunohistochemical reactions were carried out using Labeled Streptavidin-Biotin2 System-Horseradish Peroxidase (LSAB2 System-HRP) which is based on a modified labeled Avidin-Biotin (LAB) technique in which a biotinylated secondary antibody forms a complex with peroxidase-conjugated streptavidin molecules. The entire antibody complex is made visible by addition of an appropriate substrate chromogen reagent, which is converted by the peroxidase label to brown-colored precipitate at the site of antigen localization in tissue. The chromogen used is diaminobenzidine (DAB) produced by Dako (U.S.A). For positive control, normal gastric mucosa wasbenefited as internal control for Slug,lymphocytes were benefited as internal control for CD44, while sections of invasive ductal breast carcinoma positive for Her-2/neu were considered as positive control for Her-2.

Evaluation of Slug Expression: Positive expression was defined as detectable immunoreaction in the perinuclear and cytoplasmic regions of more than 10% of the tumor cells, whilst negative expression was defined as detectable immunoreaction in the perinuclear and cytoplasmic regions of less than 10% of the tumor [8].

Evaluation of CD44 Expression: CD44 expression was assessed using the widely accepted HSCORE system. Membranous +/- cytoplasmic CD44 staining was considered as positive. The evaluation of immunohistochemistry was performed in a blinded fashion by a single expert observer (KP). The proportion of neoplastic cells featuring a membranous and/or cytoplasmic staining throughout the tumor sections was assessed using a low-power magnification (x40). The HSCORE was calculated using the following equation: HSCORE=ΣPi (I), where I represents the staining intensity score (i.e. 0=no staining,1=weak staining, 2=moderate staining, and 3=strong staining) and Pi represents the percentage of stained cells (from 0 to 100%). The final HSCORE ranged from 0 to 300 and CD44 expression levels were classified as negative and positive using a cut-off value of [20].

Evaluation of Her-2/neu: Immunohistochemical staining was scored according to the criteria used in the To GA trial (Table 5). Then according to the 'magnification rule: Immunohistochemistry 3+ staining is defined as any membranous staining visible at low magnification (x5) Lateral- or U-shaped membranous staining is typically seen at cell-cell junctions. Immunohistochemistry 2+ membranous staining is visible at x10-20 magnification. Immunohistochemistry 1+staining is visible only with x40 magnification and should be considered immunohistochemistry-negative [21].

Results

This study involved 50 specimens of gastric carcinoma (Table 1). The age range of the studied patients was 29-87 years, and mean age was (56.08±12.72) years. Twenty-four cases were antral, 10 cases pyloric, 9 cases at body, 6 cases at cardia, and only 1 case at fundus. Ninteen cases were

intestinal grade II adenocarcinoma Fig. (1), eleven cases were indeterminate/intestinal grade III adenocarcinoma, 15 were diffuse carcinomas, grade IV, signet ring Fig. (2) and non-signet ring types, and 5 cases were mixed type. Of our studied cases 21 out of 50 showed lymphovascular emboli (LVE) and only 16 out of 50 showed perineural invasion (PNI). Most of the cases were advanced GC at presentation with 34% of cases were pT4, 44% were pT3, 18% were pT2 and 4% were pT 1. Lymph node metastasis was found in 41 cases; 11 cases were N1, 18 were N2 and 12 were N3. All cases were studied for Slug, CD44 and of Her2/neu immunoexpression.

Table (1): Summary of clinical data, location, classification, grading, LVE status, PNI status, staging and LN status of studied cases.

	Total No.=50
Age:	
• Mean±SD	56.08±12.72
• Range	29–87
Sex:	
• Female	20 (40.0%)
• Male	30 (60.0%)
Location:	
• Antrum	24 (48.0%)
• Body	9 (18.0%)
• Cardia	6 (12.0%)
• Pylorus	10 (20.0%)
• Fundus	1 (2.0%)
Lauren:	
• Intestinal	19 (38.0%)
• Indeterminate	11 (22.0%)
• Diffuse	15 (30.0%)
• Mixed	5 (10.0%)
Grade:	
• II	19 (38.0%)
• III	16 (32.0%)
• IV	15 (30.0%)
L. VE:	
• Negative	29 (58.0%)
• Positive	21 (42.0%)
PNI:	
• Negative	36 (72.0%)
• Positive	14 (28.0%)
Stage:	
• T1	2 (4.0%)
• T2	9 (18.0%)
• T3	22 (44.0%)
• T4	17 (34.0%)
LN:	
• N0	9 (18.0%)
• N1	11 (22.0%)
• N2	18 (36.0%)
• N3	12 (24.0%)

Immunohistochemical expression of Slug (Table 2):

Among the 50 cases of gastric carcinoma, 30 cases (60%) showed positive Slug expression Figs. (3,4) and 20 (40%) cases showed negative expression. Slug expression was associated significantly with tumor location being more in the antral and pyloric tumors (1 1 and 10 cases respectively out of the 30 positive cases) than other locations (p-value=0.011). As regard the pT stage, out of the 30 Slug positive cases 13 and 15 cases were pT3 and pT4 resepectively (p-value=0.003). Also Slug expression was significantly related to LN metastasis (p-value=0.000), as 18 and 10 cases of the 30 positive cases were N2 and N3 respectively. Slug expression showed highly significant relation with CD44 expression (p-value=0.000) as 25 cases (83.3%) of the 30 positive Slug cases were CD44 positive. We did not remark statistically significant correlation of Slug expression with age (p-value=0.954), specific gender (p-value =1.000), histopathological type (p-value=0.246), tumor grade (p-value=0.344) (taking in considreration that the expression is more in the indeterminate/high grade intestinal grade III than lower grade intestinal, grade II), lymphovascular emboli (p-value=0.160), perineural invasion (PNI) (p-value=0.120) or Her2 expression (p-value=0.3 5 1).

Immunohistochemical expression of CD44 (Table 3):

Among the 50 cases of gastric carcinoma, 29 cases (58%) expressed positivity for CD44 Figs. (5,6). There was a significant correlation with tumor location being more in the antral and pyloric tumors (18 out of the 29 positive cases; 62%) than other locations (p-value=0.023). As regard the pT stage, out of the 29 CD44 positive cases 14 and 13 cases were pT3 and pT4 respectively (p-value=017). Also CD44 expression was significantly related to LN metastasis (p-value=0.000), as 15 and 10 cases of the 29 positive cases were N2 and N3 respectively. CD44 expression showed highly significant relation with Slug expression (p-value=0.000) as 25 cases (86.2%) of the 29 positive CD44 cases were Slug positive. We did not remark statistically significant correlation of Slug expression with age (p-value =0.819), specific gender (p-value=0.413), histopathological type (p-value=0.683), tumor grade (p-value =0.478) (taking in considreration that the expression is more in the indeterminate/high grade intestinal grade III than lower grade intestinal, grade II), lymphovascular emboli (p-value=0.291), perineural invasion (PNI) (p-value=0.574) or Her2 expression (p-value=0.347).

Immunohistochemical expression of Her2/neu (Table 4):

We detected positive Her2/neu expression in 16 out of our 50 cases (32%); 6 cases showed score2

positive expression, while 10 cases showed score3 positive expression. There was a significant correlation between HER2/Neu expression and the tumor location (p=0.008); being more in the proximal tumors than other locations, as 10 out of the 16 positive cases were located in proximal sites (3 out of the 6 positive-score 2 cases were at the body, while 4,2 and 1 out of the 10 positive-score 3 cases were located at the cardia, body and fundus respectively). Her2/neu showed also significant relation with histopathological type (p-value 0.000) and grade (p-value 0.001), being more in the intestinal lower grade tumors, as 3 cases out of the 6 positive-score 2 cases were of intestinal, grade II type Fig. (7), and the other 3 out of 6 positive-score 2 were of mixed grade III tumors type, while 9 out of 10 positive-score 3 were of intestinal grade II type Fig. (8) and the last 1 out of the 10 positive-scroe 3 was of indeterminate/intestinal, grade III type. Her 2/neu expression was also significantly correlated with advanced pT stages (p-value 0.024), as 4 out of the 6 positive-score 2 cases were pT4, while 4 and 3 out of the 10 positive-score3 were pT3 and pT4 respectively. We did not remark statistically significant correlation of Her 2/neu expression with age (p-value 0. 119), specific gender (p-value 0. 177), lymphovascular emboli (LVE) (p-value 0.350), perineural invasion (PNI) (p-value 0.804), LN metastasis (p-value 0.081), Slug expression (p-value 0.322) or CD44 expression (p-value 0.161).

Table (2): Summary of clinicopathological association of Slug expression in gastric carcinoma.

	Negative Slug	Positive Slug	Test value	p-value	Sig.
	No.=20	No.=30			
Age:					
• Mean±SD	55.95±12.18	56.17±13.27	-0.058•	0.954	NS
• Range	35–79	29–87			
Sex:					
• Female	8 (40.0%)	12 (40.0%)	0.000*	1.000	NS
• Male	12 (60.0%)	18 (60.0%)			
Location:					
• Antrum	13 (65.0%)	11 (36.7%)	13.137*	0.011	S
• Body	2 (10.0%)	7 (23.3%)			
• Cardia	4 (20.0%)	2 (6.7%)			
• Pylorus	0 (0.0%)	10 (33.3%)			
• Fundus	1 (5.0%)	0 (0.0%)			
Lauren:					
• Intestinal	8 (40.0%)	11 (36.7%)	3.328*	0.344	NS
• Indeterminate	2 (10.0%)	9 (30.0%)			
• Diffuse	8 (40.0%)	7 (23.3%)			
• Mixed	2 (10.0%)	3 (10.0%)			
Grade:					
• II	8 (40.0%)	11 (36.7%)	2.646*	0.266	NS
• III	4 (20.0%)	12 (40.0%)			
• IV	8 (40.0%)	7 (23.3%)			
L. VE:					
• Negative	14 (70.0%)	15 (50.0%)	1.970*	0.160	NS
• Positive	6 (30.0%)	15 (50.0%)			
PNI:					
• Negative	18 (90.0%)	18 (60.0%)	5.357*	0.021	S
• Positive	2 (10.0%)	12 (40.0%)			
Stage:					
• T1	2 (10.0%)	0 (0.0%)	14.006*	0.003	HS
• T2	7 (35.0%)	2 (6.7%)			
• T3	9 (45.0%)	13 (43.3%)			
• T4	2 (10.0%)	15 (50.0%)			
LN:					
• N0	9 (45.0%)	0 (0.0%)	36.237*	0.000	HS
• N1	9 (45.0%)	2 (6.7%)			
• N2	0 (0.0%)	18 (60.0%)			
• N3	2 (10.0%)	10 (33.3%)			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
*: Chi-square test.
•: Independent t-test.

Table (3): Summary of clinicopathological association of CD-44 expression in gastric carcinoma cases.

	Negative CD44	Positive CD44	Test value	*p*-value	Sig.
	No.=21	No.=29			
Age:					
• Mean±SD	56.57±11.44	55.72±13.76	0.230•	0.819	NS
• Range	38–79	29–87			
Sex:					
• Female	7 (33.3%)	13 (44.8%)	0.670*	0.413	NS
• Male	14 (66.7%)	16 (55.2%)			
Location:					
• Antrum	15 (71.4%)	9 (31.0%)	11.355*	0.023	S
• Body	2 (9.5%)	7 (24.1%)			
• Cardia	2 (9.5%)	4 (13.8%)			
• Pylorus	1 (4.8%)	9 (31.0%)			
• Fundus	1 (4.8%)	0 (0.0%)			
Lauren:					
• Intestinal	10 (47.6%)	9 (31.0%)	1.496*	0.683	NS
• Indeterminate	4 (19.0%)	7 (24.1%)			
• Diffuse	5 (23.8%)	10 (34.5%)			
• Mixed	2 (9.5%)	3 (10.3%)			
Grade:					
• II	10 (47.6%)	9 (31.0%)	1.477*	0.478	NS
• III	6 (28.6%)	10 (34.5%)			
• IV	5 (23.8%)	10 (34.5%)			
L. VE:					
• Negative	14 (66.7%)	15 (51.7%)	1.116*	0.291	NS
• Positive	7 (33.3%)	14 (48.3%)			
PNI:					
• Negative	16 (76.2%)	20 (69.0%)	0.315*	0.574	NS
• Positive	5 (23.8%)	9 (31.0%)			
Stage:					
• T1	2 (9.5%)	0 (0.0%)	10.159*	0.017	S
• T2	7 (33.3%)	2 (6.9%)			
• T3	8 (38.1%)	14 (48.3%)			
• T4	4 (19.0%)	13 (44.8%)			
LN:					
• N0	9 (42.9%)	0 (0.0%)	22.446*	0.000	HS
• N1	7 (33.3%)	4 (13.8%)			
• N2	3 (14.3%)	15 (51.7%)			
• N3	2 (9.5%)	10 (34.5%)			

p-value >0.05: Non significant. *: Chi-square test.
p-value <0.05: Significant. •: Independent *t*-test .
p-value <0.01: Highly significant.

Table (4): Summary of clinicopathological association of CD-44 expression in gastric carcinoma cases.

	Her-2			Test value	*p*-value	Sig.
	0	2	3			
	No.=36	No.=6	No.=10			
Age:						
• Mean±SD	58.62±12.63	50.33±12.96	50.9±11.23	0.225•	0.119	NS
• Range	35–87	38–65	29–65			
Sex:						
• Female	14 (41.2%)	4 (66.7%)	2 (20.0%)	3.464*	0.177	NS
• Male	20 (58.8%)	2 (33.3%)	8 (80.0%)			
Location:						
• Antrum	19 (55.9%)	2 (33.3%)	3 (30.0%)	20.613*	0.008	HS
• Body	4 (11.8%)	3 (50.0%)	2 (20.0%)			
• Cardia	2 (5.9%)	0 (0.0%)	4 (40.0%)			
• Pylorus	9 (26.5%)	1 (16.7%)	0 (0.0%)			
• Fundus	0 (0.0%)	0 (0.0%)	1 (10.0%)			
Lauren:						
• Intestinal	7 (20.6%)	3 (50.0%)	9 (90.0%)	31.115*	0.000	HS
• Indeterminate	10 (29.4%)	0 (0.0%)	1 (10.0%)			
• Diffuse	15 (44.1%)	0 (0.0%)	0 (0.0%)			
• Mixed	2 (5.9%)	3 (50.0%)	0 (0.0%)			
Grade:						
• II	7 (20.6%)	3 (50.0%)	9 (90.0%)	19.350*	0.001	HS
• III	12 (35.3%)	3 (50.0%)	1 (10.0%)			
• IV	15 (44.1 %)	0 (0.0%)	0 (0.0%)			
L. VE:						
• Negative	20 (58.8%)	2(33.3%)	7(70.0%)	2.099*	0.350	NS
• Positive	14 (41.2%)	4 (66.7%)	3 (30.0%)			
PNI:						
• Negative	24 (70.6%)	4 (66.7%)	8 (80.0%)	0.436*	0.804	NS
• Positive	10 (29.4%)	2 (33.3%)	2 (20.0%)			
Stage:						
• T1	0 (0.0%)	0 (0.0%)	2 (20.0%)	14.576*	0.024	S
• T2	6 (17.6%)	2 (33.3%)	1 (10.0%)			
• T3	18 (52.9%)	0 (0.0%)	4 (40.0%)			
• T4	10 (29.4%)	4 (66.7%)	3 (33.0%)			
LN:						
• N0	6 (17.6%)	0 (0.0%)	3 (30.0%)	11.231*	0.081	NS
• N1	6 (17.6%)	2 (33.3%)	3 (30.0%)			
• N2	15 (44.1%)	0 (0.0%)	3 (30.3%)			
• N3	7 (20.6%)	4 (66.7%)	1 (10.0%)			

p-value >0.05: Non significant. *: Chi-square test.
p-value <0.05: Significant. •: Independent *t*-test.
p-value <0.01: Highly significant.

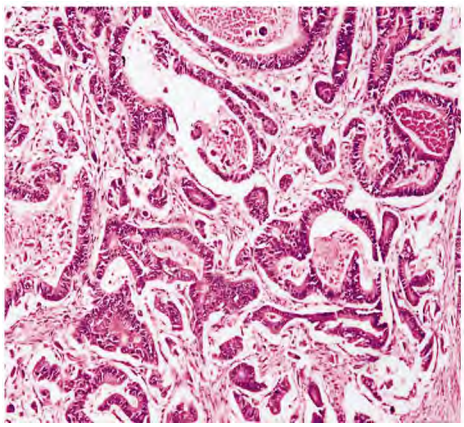

Fig. (1): Low grade intestinal (tubular) adenocarcinoma (H&E): Showed irregular, anastomosing tubules (x 100).

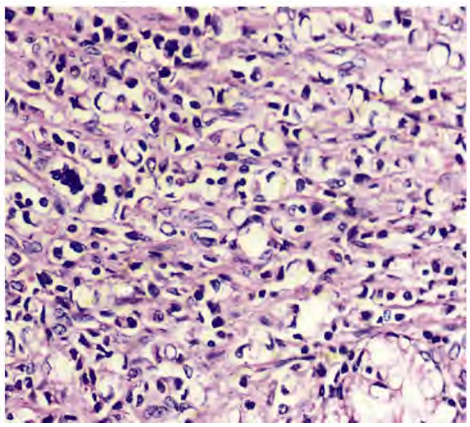

Fig. (2): Diffuse gastric carcinoma, signet ring cell type (H&E): Showing isolated or small groups of malignant cells containing intracytoplasmic mucin with eccentric nuclei (x400).

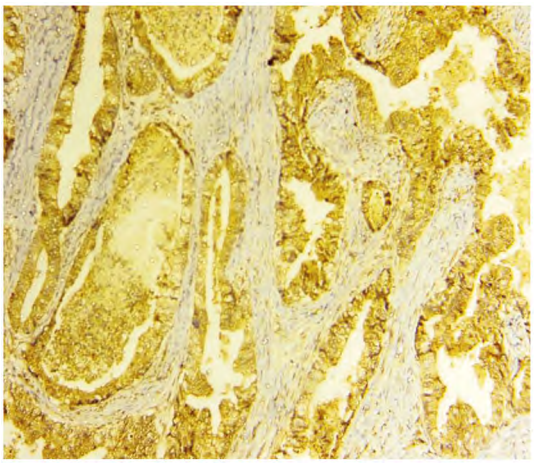

Fig. (3): Low grade intestinal adenocarcinoma, grade II (tubular) (IHC/Slug): Showed brown cytoplasmic staining of >10% of tumor cells (positive expression) (x200).

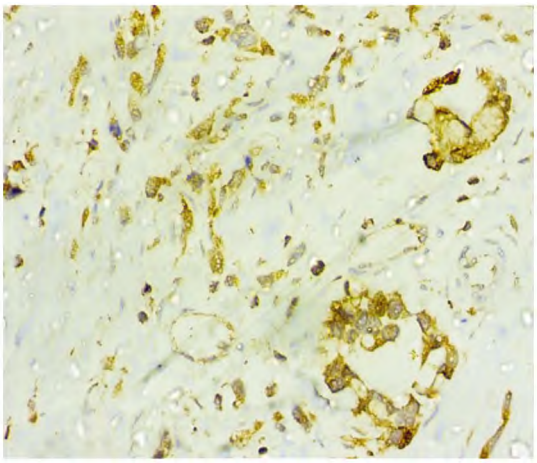

Fig. (4): Mixed gastric carcinoma, intestinal component (right) and diffuse component (left) (IHC/Slug): Showed brown cytoplasmic staining of >10% of tumor cells (positive expression) (x400).

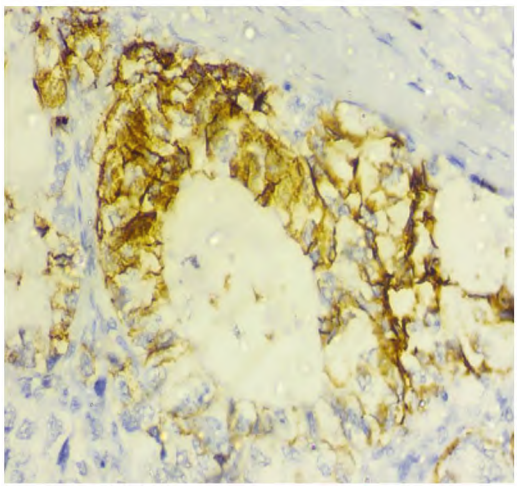

Fig. (5): Low grade intestinal adenocarcinoma, grade II (tubular) (IHC/CD44): Brown membranous and cytoplasmic staining of tumor cells (positive expression according to HSCORE) (X400).

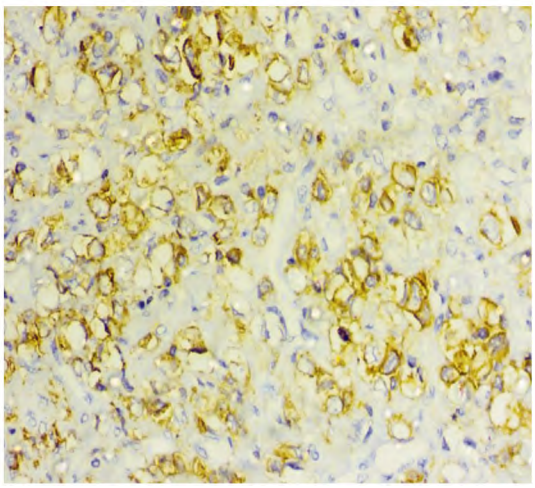

Fig. (6): Diffuse carcinoma, signet ring cell type (IHC/CD44): brown membranous and cytoplasmic staining of tumor cells (positive expression according to HSCORE) (x400).

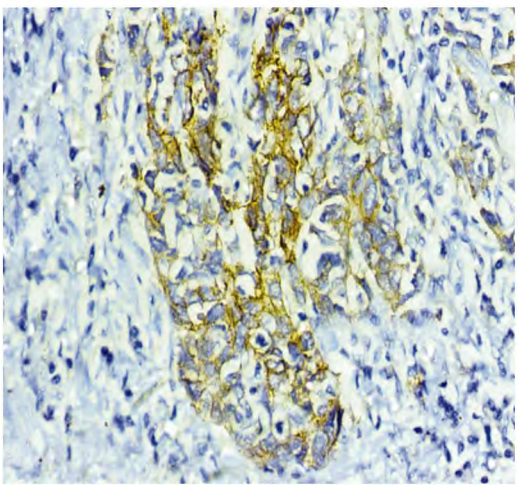

Fig. (7): Low grade intestinal adenocarcinoma, grade II (tubular) (IHC/Her2): Brown membranous staining of tumor cells (positive, score 2) (X400).

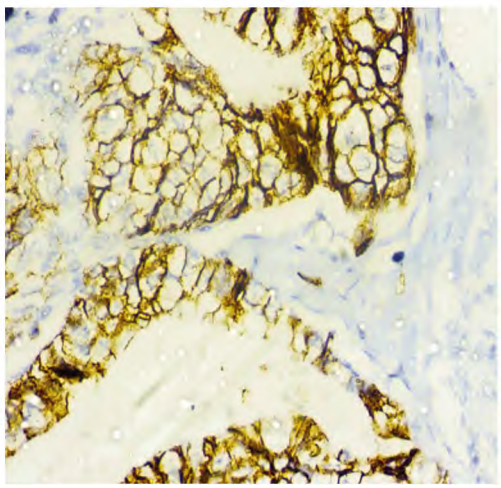

Fig. (8): Low grade intestinal adenocarcinoma, grade II (tubular) (IHC/Her2): Brown membranous staining of tumor cells (positive, score 3) (X400).

Discussion

In the current study, we revealed that the age of patients ranged from 29 to 87 years with mean of mean age of 56.08 ± 12.72. These findings are going with those of Arun et al., [22], who reported that the age of patients ranged from 32 to 70 years with mean of 52.00. Whilst American cancer society stated that the average age of people with gastric cancer when they are diagnosed is 68. About 6 of every 10 people diagnosed with stomach cancer each year are 65 or older [23].

Our results showed male predominance in carcinoma cases with male to female ratio of 3:2, which is comparable with those of Almasi, et al., [24] who resulted the ratio of 2.3; 1 and attributed this male predominance to differences in lifestyle, including drinking and smoking habits in men, which have been linked to the early development of GC. Similarly the American cancer society [23] reported that the lifetime risk of developing stomach cancer is higher in men (about 1 in 96) than in women (about 1 in 152).

As a member of the Snail superfamily of EMT-activating transcription factors (EMT-ATFs), Slug has been proved to be associated with tumor recurrence and treatment resistance both in vivo and in vitro. As a result of its important biological characteristics in cancer cells, studies about its prognostic role have been conducted in several types of tumors with controversial results [25].

In the current study, we detected positive Slug expression in 30 out of 50 studied cases (60%) and negative Slug expression 20 out of 50 studied cases (40%). That is near to the percentages in the studydone by Han et al., [26] whoreported high and moderate Slug expression in more than half of cases (51%) and low Slug expression in the remaining of the their studied cases (49%). However, Ushikado et al., [8] reported positive Slug expression in 49 out of 164 of all studied cases (29%) and negative Slug expression in remaining cases (71%). The difference observed in these results may be attributed to the different scoring systems or the number of studied cases as they conducted their study on 459 and 164 cases of GCs resepectively.

According to the obtained data, our results did not suggest the existence of a relation between the Slug expression on one hand and the age and sex of the patients on the other hand. As do most of the other studies like that of Han et al., [26]. The study of Ushikado et al., [8] stated also that no significant association between age and Slug expression, but resulted significant association between male gender and negative Slug expression (p-value: 0.016).

Comparison of Slug immunostaining with the tumor location, showed that most of the Slug-positive tumor cases are located at the antrum (1 1 out of 30 cases) and the pylorus (10 out of 30 cases) with statistically significant relation between the location of tumors and positive Slug expression (p-value 0.011). It is worthy noting that the study of Han et al., [26] who mentioned this parameter in their results stated that no statistically significant relation between location of the tumor and Slug expression (p-value 0.599).

From the point of view “tumor classification/ grade of differentiation”: In the present study, as regard the whole cases collectively, insignificant relation between Slug expression and degree of tumor differentiation (p-value 0.344) was noticed. These results were consistent with those reported by Han et al., [26] in which also insignificant relation was found between degree of tumor differentiation (regarding the whole cases collectively) and Slug expression. In our study, as regard intestinal type adenocarcinomas separately, the relation was statistically significant, as the Slug expression increase in well differentiated, grade II and poorly differentiated, grade III adenocarcinomas, but the Slug expression decreases in the grade IV tumors (diffuse/poorly cohesive; signet ring and non-signet ring carcinomas), and these results are also going with their study Han et al., [26] as regarding the adenocarcinomas, as they stated statistically significant relation between Slug expression and grade of differentiation of adenocarcinomas, but also with decrease Slug expression in grade IV tumors as in our study. On the other hand, the study conducted by Ushikado et al., [8] stated that the relation between Slug expression and tumor classification/ grade of tumor is statistically insignificant in all tumor types/grades.

In the present study, insignificant relation between Slug expression and tumor lymphovascular invasion (p-value=0.160) was noticed. These results are going with the results of Han et al., [26] who ruslted also an insignificant relation (p-value 0.055). While the study of Ushikado et al., [8] resulted significant relation (p-value 0.0017). These variations may be attributed to the different numbers of cases and serial sections between the studies.

Significant relation between Slug expression and tumor perineural invasion (p-value=0.021)

was noticed in our study. These results are near to the results of Han et al., [26] who ruslted also an significant relation (p-value<0.001).

Evaluation of Slug expression in relation to the infiltration depth of the primary tumor showed highly significant results (p-value=0.003), where positive Slug expression was observed in 15 out of 30 and 13 out of 30 positive Slug cases of locally advanced stages (pT3&pT4) and in 2 out of 30 positive Slug cases of early stage (pT2). Our findings agreed with those reported by Han et al., [26] who stated the presence of highly significant relation between Slug expression and pT-stage (p-value <0.0001). And also near to Ushikado et al., [8] who stated near results (p-value=0.49). This discordance can be explained by different scoring systems used in different studies or different sample sizes leading to conflicting results.

The relation between Slug expression and LN metastasis was statistically highly significant in our study (p-value 0.000). Our data were consistent with the study done by Ushikado et al., [8] (p-value 0.0083). And non-contradicting with the study of Han et al., [26] who found also a significant relation between Slug expression and LN metastasis.

Highly significant relationship between Slug and CD-44 expression (p-value=0.000) was observed in our study. This is going with the study of Gui-Fang et al., [27] who resulted strong association between EMT markers expression and CD-44 (CSCs marker) expression.

Non-significant relationship between Slug and Her-2 neu expression (p-value=0.3 5 1) was observed in our study. Unlike the results conducted on the breast cancers which suggested that Her-2 can lead to enhanced stemness through induction of EMT, with strong association between the three types of markers, like that study conducted by Parul and Sanjay [28]. This discordance can be explained by different tissues (stomach and breast), different scoring systems used in different studies, different numbers of cases or different sample sizes, leading to conflicting results.

The current study detected a high frequency of CD44 expression among the different gastric carcinoma types (58% of tumors). This finding was near to the results of Hanaa et al., [29] who reported positive expression of CD44 in 55% of cases, Near to the result of Dhingra et al., [30] who found that CD44 expression was 51% in the tumor. Also these findings are in concordance with those of Yuan et al., [31] who reported the frequency of CD44 positive cells in tumor samples was 60%. Unlike result obtained by Cao L et al., [32] who detected the expression of CD44 in 46.3% of gastric carcinoma specimens, and found that the percentage of CD44 positive cells per specimen was less than 15% in 97.5% patients.

We evaluated our results of CD44 protein expression and clinico- pathological characteristics of gastric Cancer such as age, sex, location of tumor, histologic type, grade and pathological TNM stage. The findings may help to select patients at high risk For tumor development who might benefit from surveillance follow-up for gastric cancer.

We did not remark statistically significant correlation of CD44 expression with age or specific gender (p-value= 0.819&0.413 respectively) matching with results reported by Cao L et al., [32] where (p-value>0.05). This contrast to Ryu et al., [33] who mentioned significant correlation with age >60 years. That may have had an influence on the association of CD44 expression with old age [34].

According to the obtained data, our results suggest existence of a relation between the CD44 expression and the tumor's location as most of the CD-44-positive tumor cases are located at the antrum and pylorus (18 out of 29 cases/62%) with (p-value 0.023). Senel et al., [35] have mentioned similar results with incidence of positive CD44 expression was 66.7% in distal locations. And also concordant to the result obtained by Tongtawee et al., [36] who found that location of tumor (distal) was significantly related to CD44 protein expression (p-value=0.018).

CD44 evaluation depending on the histological type has shown no significant statistical results. This finding matching with results mentioned by Senel et al., [35] and Hanaa et al., [29]. In contrast to the result obtained by Ryu et al., [33] and Li et al., [37] who reported that CD44 positivity was higher in intestinal type than in diffuse type gastric cancer. On the other hand, Min et al., [38] reported that CD44 expression correlated with diffuse type adencarcinoma.

CD44 positivity and tumor grade showed no significant statistical correlation (p=0.478), this was in agreement with the review of Senel et al., [35] And in contrasting with results obtained by Hanaa et al., [29], Cao L et al., [32] and Wang et al., [39] who recorded CD44 positivity with higher rate of expression in high grade tumors. However, Yamaguchi et al., [39] found that the expression of the CD44 protein was significantly higher in dif-

ferentiated adenocarcinoma than in poorly differentiated one. This variation may contribute to the use of various antibodies having subtle differences in specificity and thus increasing the possibility of cross-reactivity between the antibodies. Another reason for such discrepancies is probably the comparison of results having different techniques Zavrides et al., [41].

In our study CD44 expression was correlated with increase depth of invasion of tumor with (p-value=0.017), where the CD44 expression was detected in T4 and T3 than in T2. This matching with result obtained by Hanaa et al., [29] and Chen et al., [42] all reported that the CD44 expression was positively correlated with advanced stage and in contrast to Cao L et al., [32] and Li et al., [37] studies which proved that there is no significant difference in CD44 expression level in relation to stage of tumor.

In the present study, insignificant relation between CD-44 expression and tumor lymphovascular invasion (p-value=0.291) was noticed. These results are going with the results of Kengo et al., [43] who resulted also an insignificant relation (p-value= 0.44).

Also noticed in our study an insignificant relation between CD-44 expression and tumor perineural invasion (p-value=0.574).

Another highly significant correlation was observed between CD44 expression and nodal metastasis. The CD44 immunohistochemical expression was noted more frequently in prescence of lymph node metastasis with the more positivity observed in N3 more than N2&N1 with (p-value=0.000) The significant correlation between the CD44 expression and prescence of LN metastasis is also signaled by Chen et al., [42] Hanaa et al., [29] and Ryu et al., [33]. This contrasts with results obtained by Kengo et al., [43] and Lu et al., [44].

As mentioned above highly significant relationship between Slug and CD-44 expression (p-value =0.000) was observed in our study. This is going with the study of Gui-fang et al., [27] who resulted strong association between EMT markers expression and CD-44 (CSCs marker) expression. And non-significant relationship between Slug and Her-2 neu expression (p-value=0.3 5 1) was observed in our study. Unlike the results conducted on the breast cancers which suggested that Her-2 can lead to enhanced stemness (CD-44 expression) through induction of EMT, with a storng association between the three types of markers, like that study conducted by Parul and Sanjay [28]. This discordance can be explained by different tissues (stomach and breast), different scoring systems used in different studies, different numbers of cases or different sample sizes, leading to conflicting results.

In our study, Her-2 positivity was observed in 16 out of our 50 cases (32%) (6 cases as score 2 and 10 cases as score 3). This is going with the range of the results obtained by most of the similar studies as that of Gravalos & Jimeno, [45] who mentioned that some series reported a 9%-38% of Her-2 positive tumors, and actually his results was falling in this range.

We did not remark statistically significant correlation of Her-2 positivity with age or specific gender (p=0.119) matching with results reported by Shan, et al., [46]. This contrast to Indu, et al., [47] who mentioned significant correlation with male gender but this was explained as this may be attributed to greater number of male patients in his study as gastric adenocarcinomas are more common in males.

Her-2 positivity was higher in GEJ carcinoma than in disital GC (62.5% vs. 37.5%) (p>0.008) similar to results obtained by andGravalos & Jimeno [45] and, Leni, et al., [48] who reported that (25%) Her-2 positivity in GEJ carcinoma Vs. (9.5%) in disital GC. On the other hand, Nicola, et al., [49] found no statistically significant correlation among Her-2 overexpression and tumor site. He have mentioned that the high prevalence of antral cancers in his cohort has limited the statistical evaluation of differences between tumors arising in the GEJ and disital counterpart.

Statistically significant differences in immunohistochemically detected Her-2 overexpression were noted between the tumor subgroups. Significantly greater proportion (75%) of intestinal-type tumors showed positive expression, 3 cases also of indeterminate/intestinal type grade III and only one case of diffuse type. These findings correlate well with Indu, et al., [47] who recorded a total absence of Her-2 expression in diffuse type gastric cancer. He attributed this to the smaller number of diffuse type of gastric cancers in his study. Also, geographic variation as a reason for negative Her-2 expression in diffuse type was accepted explanation to Indu, et al., [47].

Her-2 positivity and tumor grade showed significant statistical correlation (p=0.001), in concordance with results obtained by Tafe et al., [50] and Shan, et al., [46] who recorded Her-2 expression with more frequency in well and moderately dif-

ferentiated adenocarcinoma. This contrasting with results obtained by Leni, et al., [48] who recorded Her-2 positivity with higher rate of expression in high grade tumors with high Ki-67 labeling index; thus it represents an additional morphological parameter reflecting aggressiveness of GC Leni, et al., [48].

We found that the relation between the tumor LVE and PNI in one hand and Her-2/neu expression on the other hand was proved to be statistically insignificant (p-values 0.863 and 0.746 respectively). This is concordant to the results obtained by the study conducted by Tev fiket., al, [51].

Statistically significant correlation was found between Her-2 positivity and depth of tumor invasion in our study, (p-value=0.024), as most of the Her-2/neu-positive cases (11 out of 16) are either T3 or T4, matching with the earlier study as stated by Chao, et al., [52] who reported lower rate of Her-2 positivity in early gastric cancer (10.4%) and in contrast to the study conducted by Moelans, et al., [53] who reported adverse results and attributed this to the well differentiated nature of the Her-2 positive tumors with lower propensity to discohesion and invasion.

There was a non-significant relationship between LN metastasis and Her-2/neu expression (p value=0.81). In contrast to studies done by Ling, et al., [54] and Antonio, et al., [54] who reported a significant relationship and high level of concordance in Her-2 status between primary GC and corresponding lymph node metastases.

Again, as mentioned above a non-significant relationship between Slug and Her-2/neu expression (p-value=0.3 5 1) was observed in our study. Unlike the results conducted on the breast cancers which suggested that Her-2 can lead to enhanced stemness through induction of EMT, with a strong association between the three types of markers, like that study conducted by Parul and Sanjay [28]. This discordance can be explained by different tissues (stomach and breast), different scoring systems used in different studies, different numbers of cases or different sample sizes, leading to conflicting results.

Conclusion:

This study revealed that Slug, CD44 and Her-2/neu expressions were directly related to stage of tumor and may be associated with tumor progression in gastric cancer pathogenesis. Therefore, they could be of valuable significance in predicting aggressive invasive gastric carcinomasand in determining the prognosis in such cases.

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التعبير المناعى الهستوكيميائى لكل من (سلج)، (سى دى ٤٤) و (هير٢/نيو) فى سرطان المعدة

خلفية البحث: أهم العوامل النذيرة الخاصة بسرطان المعدة هى درجة اجتياحه لجدار المعدة ودرجة تمايز الخلايا السرطانية، وعلى الرغم من ذلك فإنه لا يوجد عامل مؤثوق به يمكنه التكهن أى الحالات عرضة لتفاقم او عودة الورم. وذلك فالدلالات الجزيئية مطلوبة للتقييم الفردى او الشخصى لتوقعات سير المرض ولتحديد العلاج الفعال.

الهدف من البحث: الهدف من هذه الدراسة هو تقييم التعبير المناعى لكل من (سلج)، (سى دى ٤٤) و (هير٢/نيو) فى سرطان المعدة وتحديد العلاقة بينهم وبين الدلالات الباثولوجية الأكلينيكية والعلاقة بين بعضهم البعض، مما يساهم فى تقييم توقعات سير المرض.

المواد وطرق البحث: تم تقييم التعبير المناعى لكل من (سلج)، (سى دى ٤٤) و (هير٢/نيو) فى خمسين حالة من حالات سرطان المعدة، تم تجميعهم من ملفات معامل الباثولوجيا الجراحية بمستشفيات جامعة الأزهر فى الفترة من نوفمبر٢٠١٧٧٧٧٧ إلى فبراير٢٠٢١. هذه العينات تم الحصول عليها عن طريق الاستئصال الجذرى للمعدة.

نتائج البحث: كان هناك دلالة إحصائية مهمة بين التعبير المناعى لكل من (سلج) و (سى دى ٤٤) فى سرطان المعدة و مواقع الاورام البعيدة ومرحلة اختراق الورم ومرحلة انتشار الاورام للغد الليمفاوية. بينما كانت هناك دلالة إحصائية ممهمة بين تعبير (هير٢/نيو) و مواقع لاورام القريبة والنوع مع رجة تباين الاورام ومرحلة اختراق الاورام ايضا.

الاستنتاج: هناك علاقة طردية بين التعبير المناعى لكل من (سلج) و (سى دى ٤٤) و (هير٢/نيو) وبين مرحلة سرطان المعدة. وبالتالى يمكن استخدامهم فى توقع السلوك العدوانى الانتشارى للاورام وبالتالى تحديد الخيارات العلاجية المناسبة.