Programmed Death Ligand -1 Expression and Gastric Mucosal Nodularity as an Indicator of *Helicobacter Pylori* Associated Gastritis and Gastric Carcinoma

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Background and study aim: Gastritis linked to *Helicobacter pylori* is characterized by its high frequency, drug resistance and development to gastric cancer. We aimed to examine the role that endoscopic nodule appearance and expression of programmed death ligand 1 (PD-L1) have in diagnosis of gastric cancer and *H. pylori*-associated gastritis.

Patients and Methods: Three groups participated in this prospective case-control study: Twenty patients with gastric cancer were in group II, twenty patients with positive *H. Pylori* infection were in group III, and twenty patients with seemingly normal gastric tissue were in group I. Of these, eighteen cases had mucosal nodularity, and twenty-two instances did not. A research using PDL-1 primary antibody immunohistochemistry was carried out on all groups.

Results: Gastric mucosal nodularity was a significant finding in *H. pylori* infection; however, it did not affect clinical disease severity when compared to those without nodularity (p> 0.05). PDL-1 expression was found in 27.5% of *H. pylori* patients and 50% of gastric carcinoma cases, respectively. PDL1 combined positive score (cps) was statistically higher in *H. pylori* group than in control group (p =0.015). However, there was no statistically significant difference in PDL-1 levels based on illness severity (p> 0.05). Furthermore, PDL1 cps in gastric cancer group was significantly higher than in control and *H. pylori* groups (p < 0.001 and p = 0.041, respectively).

Conclusions: Although it is a worrying sign of *H. Pylori* infection, gastric mucosal nodularity is not very predictive. From *H. pylori* infection to stomach cancer, PDL-1 expression rose gradually.

INTRODUCTION

Human stomach epithelium is specifically colonised by gram-negative bacterium Helicobacter pylori, sometimes known as H. Pylori. Marshall and Warren identified H. pylori in 1983 when it was exposed to the stomach epithelium of chronic gastritis patients. They later received the 2005 Nobel Prize in Medicine in recognition of their identification of this harmful bacterium and its connection to peptic ulcer disease [1].

Chronic gastritis is linked to H. pylori and atrophy, metaplasia, dysplasia and malignancy. Consequently, it has been suggested that treating atrophic gastritis and peptic ulcers as well as preventing stomach cancer can be achieved by eliminating the H. pylori infection [2].

It has long been hypothesized that H. pylori infection may alter the gastric mucosal endoscopic appearance, giving endoscopists important diagnostic data. Early research in this field showed that the stomach's collecting venules in H pylori infection changed visibly [3].

The RAC (Reguar Arrangement of Collecting Venules), which is evident by attentive inspection without the need for magnification, has been confirmed as a substantial endoscopic predictor of H pylori-naïve stomach in the present era of high-definition

endoscopy. Additional mucosal characteristics that have been suggested to predict the presence of H pylori include diffuse erythema, linear erythema, gastric erosions, mucosal edema, swollen gastric folds, the mosaic appearance of the mucosa, mucosal atrophy, fundic gland polyps, intestinal metaplasia and gastric antral nodularity [3]. The features of the gastric mucosa on endoscopic pictures in chronic gastritis vary depending on the length and severity of the H. pylori infection. Chronic gastric mucosal inflammation and H. pylori infection are linked to endoscopic findings of diffuse redness, increased folds, nodularity, atrophy and intestinal metaplasia [4].

Children's stomachs exhibit nodularity far more commonly than those of adults, which could indicate an early H. pylori infection. Compared to the corpus mucosa, the antral mucosa exhibits nodularity more frequently [5].

Although the exact process is uncertain, H. pylori also cause gastric epithelial cells to express programmed death ligand 1 (PD-L1). A protective ligand called PD-L1 is known to inhibit the T cell effector function, which suppresses the immune system. Premalignant lesions that eventually lead to gastric cancer may be created by H. pylori-infected cells that express PD-L1. These cells may be immune system-protected [6]. Therefore, the justification for PD-L1 preventative and potential targeted therapeutics stems was explained by the possibility that the detection of PD-L1 expression is an early event in the development of gastric cancer.

Thus, our goal was to find out how PD-L1 expression and an endoscopic nodule-like appearance helped identify stomach cancer and H. pylori-associated gastritis.

PATIENTS AND METHODS

Study Population and Randomization:

This study had 60 patients who were candidates for upper endoscopy and were between the ages of 18 and 75. It was a prospective case-control study; the National Liver Institute's endoscopic unit provided the data. Stool analysis and histological investigation were combined to identify the presence of H. pylori infection. Furthermore, as a control group, PDL-1 expression was assessed in twenty normal stomach mucosal tissues. This group is not included in endoscopic or clinical comparisons.

Three categories were created from the cases: group I included 40 patients with positive H. Pylori, which were further split into two groups based on the nodularity found during an endoscopic examination; group II included 20 patients whose gastric carcinoma was confirmed through an endoscopic biopsy; and group III included 20 patients whose gastric mucosal tissue appeared to be normal (obtained either endoscopically or from non-tumor gastric tissue in the case of a Whipple operation).

Cases of adults who aged from 18 to 75 who were deemed appropriate for upper endoscopy and had their first H. pylori infection confirmed were included. Patients with H. pylori who had already received therapy and pediatric cases were not included in the study. Additionally, patients with stomach cancer who received neoadjuvant therapy or who underwent gastrectomy were excluded from the study.

Laboratory investigation:

Hemoglobin, platelets count, white blood cells (WBCs), creatinine and H. pylori antigen test in stool were performed .

Endoscopic evaluation of H. pylori group:

Cases of H. pylori were evaluated endoscopically for diffuse redness, antral nodularity, increased gastric folds, and sticky, persistent mucus.

When endoscopic examination reveals a nodular or diffuse miliary pattern of tiny elevations in the gastric mucosa, primarily in the antrum and sometimes throughout the entire gastric body, it is referred to as gastric mucosal nodularity [7]. According to several research, the presence of antral nodularity is significantly predictive of H. pylori infection [8].

Histopathological evaluation of the studied cases:

The modified Sydney methodology was used to perform H. Pylori histology. This method documented five histologic variables: intestinal metaplasia, atrophy, chronic inflammation, activity and H. pylori density [9]. Sydney System, as it has been updated. 1994 Houston, Texas: International Workshop on the Histopathology of Gastritis. Giemsa stain: After deparaffinizing and rehydrating the sections, a ready-to-use Giemsa's solution is applied to the slides and left for 5 minutes before being washed with distilled water for 10 seconds. The blue

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stain of H. pylori was visible adjacent to the gastric mucosa.

Based on the World Health Organization (WHO) classification of gastrointestinal tract (GIT) tumors, the pathological grade (low or high grade) and histological type (tubular/intestinal type, poorly cohesive type, mixed type, or others) of patients with gastric cancer were evaluated histologically [10].

The immunohistochemical staining and assessment of PDL-1 antibody expression:

Primary antibody clone E1L3N (Cell Signaling Technology, Danvers, USA) was used for PDL-1 primary antibody immunostaining at a dilution of 1:400. In order to retrieve the antigen, a high PH tris-EDTA solution (Dako, Ref K8000, Glostrup, Denmark) has to be heated for 20 minutes and then cooled for an additional 20 minutes. An equation that took into account both the expression in associated immune cells and epithelial cells was used to determine the PD L-1 combination positive score (CPS). We attempted to adhere to the PDL1 scoring parameters for gastric cancer. The PDL1 CPS is the reliable approach to determining PDL1 expression in gastrointestinal cancer. The PD L-1 CPS was calculated using an equation that considered the expression in epithelial cells as well as the related immune cells. Tumour cells with cytoplasmic staining, neutrophils, eosinophils, plasma cells, stromal cells, necrotic cells, and cellular debris should be eliminated from the numerator when computing the CPS. Different cut-off values (CPS 1, 5, 10) are investigated. The cases were considered as negative (<1%) or positive (≥1%) [11].

Statistical analysis

A social science statistical tool (SPSS 22.0, IBM/SPSS Inc., Chicago, IL) was used to statistically analyse the results. For data that was regularly distributed, descriptive statistics were shown as mean (X) and standard deviation (SD). The method for presenting qualitative data was frequency with percentage (%). When comparing two or more groups with respect to a single qualitative variable, the Pearson Chi-square ($\chi 2$) test was employed. When comparing two or more groups on a single qualitative variable, the Montecarlo test was employed. For continuous data, a one-way ANOVA test was employed to look for meaningful differences between more than two groups with normal distributions. The results were deemed significant at the $p < 0.05$ level.

RESULTS

Compared to the H. pylori group, the gastric cancer group was statistically older. The cancer group had a higher prevalence of males than the H. pylori group. Regarding socioeconomic level, the prevalence of diabetes, and abdominal pain, there was no statistically significant difference between the groups under investigation. Compared to the H. pylori group, the cancer group exhibited a higher prevalence of hypertension (HTN) (p= 0.030). In comparison to the H. pylori group, the cancer group experienced greater cases with both appetite loss and weight loss (p< 0.001), Table 1

The cancer group's haemoglobin levels were statistically considerably lower than the H. pylori group's (p= 0.001). There was no significant variation in platelet counts between the H. pylori group and cancer group (p= 0.362). The cancer group's WBC levels were statistically greater than the H. pylori group's (p= 0.017). The cancer group's creatinine levels were statistically significantly greater than the H. pylori group's, Table 2 .

No one in the control group has gastritis, gastroesophageal reflux (GERD) or sliding hiatus hernia (HH). The H. Pylori group was substantially linked to a high incidence of sliding HH in contrast to the cancer group (p= 0.015). Moreover, nodularity was a pathognomonic sign in H. Pylori patients (n=18 [45%], p <0.001) Table 2 .

The histological type of gastric carcinoma cases was as follows: 20% had poor cohesive tissue, one had mixed intestinal and poorly cohesive tissue, 70% had tubular/intestinal tissue, and the remaining case was mucinous. Additionally, 40% of cases had a high pathological grade and 60% had a low pathological grade. The histology results in the patients under investigation were shown in Figure 1.

The relationship of endoscopic nodularity and the histopathological findings of H. pylori cases:

Based on pathological data, there was no statistically significant correlation seen in the H.

Pylori group between the severity of the disease and endoscopic findings of nodularity, Table 3.

The immunohistochemical expression of PDL-1 in the studied cases:

PDL-1 expression was absent in the control group, positive PDL-1 cps expression was found in 27.5% of cases of H. pylori-associated gastritis, and positive PDL-1 cps expression was found in 50% of cases of gastric cancer, Figure 2.

The PDL1 cps in the H. pylori and control groups was significantly lower than that of the cancer group ($p < 0.001$ and $p = 0.041$, respectively). In addition, PDL1 in the H. pylori group was statistically greater than in the control group ($p = 0.015$), Table 4.

The relationship of PDL-1 expression and the histopathological findings of the studied cases: Based on the severity of the disease, there was no statistically significant difference in PDL-1 levels in the H. pylori group ($p > 0.05$). Additionally, PDL-1 expression did not significantly correlate with the histological type or grade of gastric cancer ($p = 0.351$ and $p = 0.966$, respectively).

Table 1: Comparison of the demographic data, DM, HTN, and clinical presentation between the study groups

Variables		Group 2 (H. Pylori) (n= 40)	Group 3 (Cancer) (n= 20)	P-value
Age (years) [Mean ± SD]		42.55 ± 13.60	64.05 ± 8.15	P< 0.001*
Gender [n (%)]	Male	19 (47.5%)	14 (70%)	P= 0.042*
	Female	21 (52.5%)	6 (30%)	
Socioeconomic status [n (%)]	Low	24 (60%)	13 (65%)	P= 0.704
	High	16 (40%)	7 (35%)	
DM		8 (20%)	7 (35%)	P= 0.286
HTN		6 (15%)	9 (45%)	P= 0.030*
Clinical presentation				
Abdominal pain		39 (97.5%)	20 (100%)	P= 0.939
Loss of appetite		14 (35%)	20 (100%)	P< 0.001*
Weight loss		5 (12.5%)	20 (100%)	P< 0.001*

SD= Standard deviation, DM= Diabetes mellitus, HTN= Hypertension, *= significant

Table 2: Comparison of the laboratory, endoscopic and pathological data in the study groups

Variables	Group 2 (H. Pylori) (n= 40)	Group3 (Cancer) (n= 20)	P value
Hemoglobin (gm/dL) [Mean ± SD]	11.87 ± 1.33	10.36 ± 1.58	P= 0.001*
PLTs(10^3/ml) [Median (Range)]	329 (144 – 564)	279 (176 – 455)	P= 0.362
WBCs (10^3/ml) [Median (Range)]	6.7 (3.5 – 12.4)	9.8 (4.6 – 59)	P= 0.017*
Creatinine (mg/dL) [Median (Range)]	0.9 (0.6 – 1.6)	1.4 (0.8 – 2.88)	P < 0.001*
Endoscopic findings			
No GERD	27 (67.5%)	14 (70%)	P= 0.746

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GERD class a	7 (17.5%)	4 (20%)	
GERD class b	6 (15%)	2 (10%)	
Sliding HH [n (%)]	19 (47.5%)	15 (75%)	P= 0.015*
Gastritis [n (%)]	40 (100%)	0(0%)	P= 1
Nodularity [n (%)]	18 (45%)	0 (0%)	P< 0.001*

PLTs= Platelets, HH= Hiatus hernia, GERD= Gastroesophageal reflux disease, *= significant

Table 3: Disease severity according to pathological findings in the H. Pylori group

Variables		No nodularity (N=22)	Nodularity (N=18)	P value
H. Pylori score	Mild	8 (36.4%)	9 (50%)	P= 0.450
	Moderate	9 (40.9%)	4 (22.2%)	
	Marked	5 (22.7%)	5 (27.8%)	
Chronic Inflammation	Mild	4 (18.2%)	3 (16.7%)	P= 0.798
	Moderate	14 (63.6%)	13 (72.2%)	
	Marked	4 (18.2%)	2 (11.1%)	
Lymphoid aggregate/follicles	Absent	5 (22.7%)	3 (16.7%)	P= 0.887
	Present	11 (50%)	10 (55.6%)	
	Prominent	6 (27.3%)	5 (27.8%)	
Activity	Absent	3 (13.6%)	1 (5.6%)	P= 0.654
	Mild	11 (50%)	8 (44.4%)	
	Moderate	5 (22.7%)	7 (38.9%)	
	Marked	3 (13.6%)	2 (11.1%)	
Antral atrophy	Absent	17 (77.3%)	14 (77.8%)	P= 0.358
	Mild	3 (13.6%)	4 (22.2%)	
	Moderate	2 (9.1%)	0 (0%)	
Antral metaplasia	Absent	19 (86.4%)	18 (100%)	P= 0.103
	Mild	3 (13.6%)	0 (0%)	
Hyperplasia	Absent	19 (86.4%)	17 (94.4%)	P= 0.397
	Focal	3 (13.6%)	1 (5.6%)	

Table 4: Comparison of PDL-1 expression in the studied groups

Variables	Group 1 (Control) (n= 20)	Group 2 (H. Pylori) (n= 40)	Group3 (Cancer) (n= 20)	P value
Combined positive score [n (%)]				
<1	20 (100%)	29 (72.5%)	10 (50%)	P1=`0.015* P2 < 0.001* P3= 0.041*
1≥cps<5	0 (0%)	9 (22.5%)	3 (15%)	
5≥cps<10	0 (0%)	1 (2.5%)	4 (20%)	
≥10	0 (0%)	1 (2.5%)	3 (15%)	

P: General intergroup significance, P1: Comparison between Group 1 (Normal group) and Group 2 (H. Pylori group), P2: Comparison between Group 1 (Normal group) and Group 3 (Cancer group), P3: Comparison between Group 2 (H. Pylori group) and Group 3 (Cancer group), *: Statistically significant (p< 0.05).

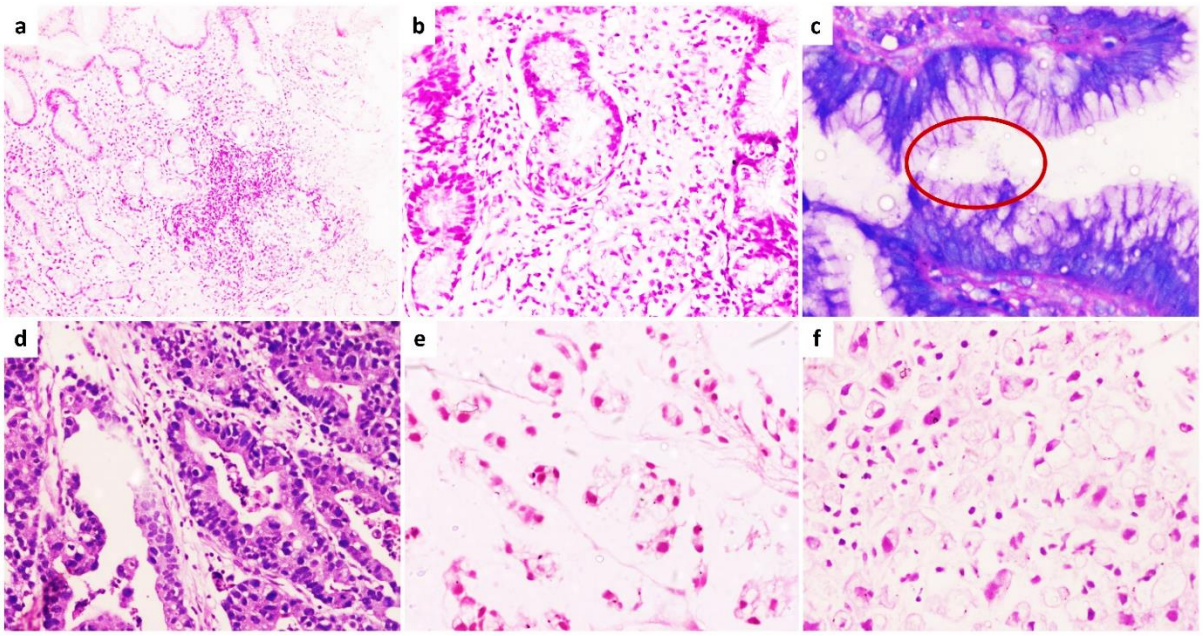

Figure 1: Histopathological features of the studied cases: a) A case of H. pylori gastritis showed moderate chronic inflammation with lymphoid follicle formation (H&E 100x), B) A higher power view showed moderate activity with neutrophils attacking gastric glands (H&E 200x), c) H. pylori infection is highlighted by Geimsa stain as cord-like structures attached to the mucin (Giemsa stain 400x), d) A case of low-grade gastric adenocarcinoma arranged in tubule-papillary pattern (H&E 200x), e) A case of low-grade gastric mucinous carcinoma arranged in clusters floating in lakes of mucin (H&E 200x), f) A case of poorly cohesive gastric carcinoma arranged in discohesive cells of signet ring phenotype (H&E 400x).

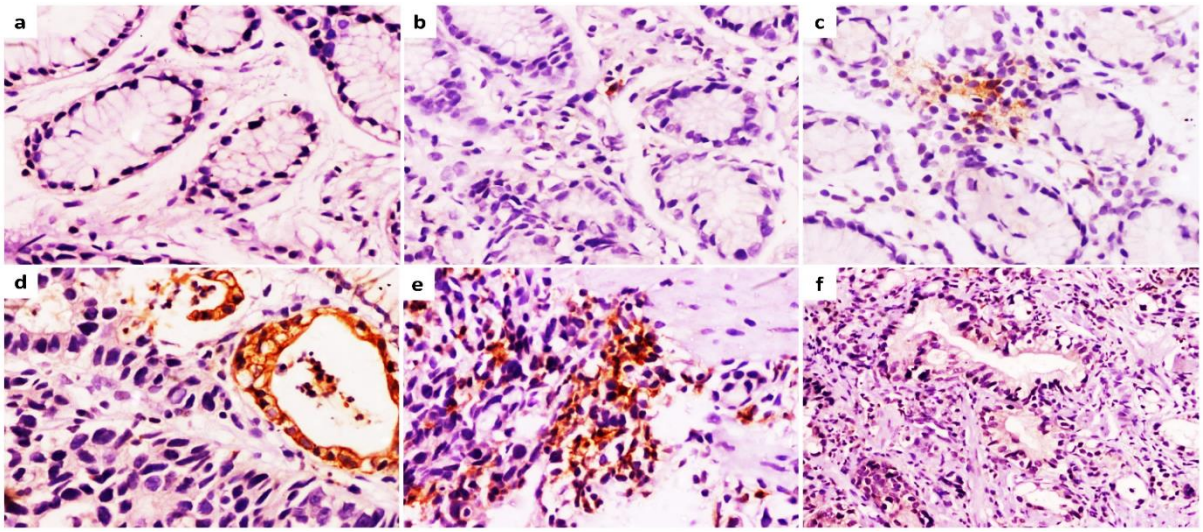

Figure 2: The immunohistochemical expression of PDL1 in the studied groups: a) A case of normal gastric tissue shows negative PDL1 expression (IHC 200x), b) A case of H. pylori gastritis shows PDL1 cps score < 1% of inflammatory cells (IHC 200x), c) A case of H. pylori gastritis shows PDL1 cps score (1≥cps<5) in inflammatory cells (IHC 200x), d) A case of gastric carcinoma shows PDL1 cps score of 5≥cps<10 in tumor cells and negative in inflammatory cells (IHC 400x), e) A case of gastric carcinoma shows PDL1 cps score of 5≥cps<10 in inflammatory cells and negative in tumor cells (IHC 400x), f) A case of gastric carcinoma shows PDL1 cps negative in both tumor and inflammatory cells (IHC 200x).

DISCUSSION

Helicobacter pylori (H. pylori) is a human pathogen that is significant responsible for variety of illnesses, including peptic ulcers, gastritis, mucosa-associated lymphoid tissue lymphoma and gastric cancer [12].

There are two main ways that H. pylori-associated carcinogenesis happens: directly and indirectly. The former are caused by long-term inflammation, which raises cell turnover and accumulates mitotic mistakes, and by the production of regulatory T cells, which suppresses the immune system [13].

Our research revealed that the cancer group's age was statistically substantially greater than that of the H. pylori and normal groups. In addition, the normal group age was higher than the H. Pylori group. In comparison to the H. pylori group, there was a higher male predominance in the cancer and normal groups. Between the three study groups, there was no statistically significant variation in the socioeconomic status.

Zhao et al. included 315 patients with colorectal adenomatous polyp (CAP), and 207 participants were categorized as healthy controls, which is consistent with our study. The CAP group was found to be older ($p < 0.001$) than the control group. Both groups were predominately made up of men, although the CAP group had a much larger percentage of females than the control group ($p < 0.001$) [14].

According to our research, there was no statistically significant variation in the prevalence of stomach discomfort among the cases. Compared to the H. pylori group and the control group, Weight loss and decreased appetite were more common in the cancer group.

Following H. pylori eradication medication, Zaman et al. noticed alterations in the antigen test findings and found H. pylori antigens in the faeces of symptomatic patients. Samples of blood, urine, and faeces were taken from sixty-two dyspeptic patients. 52% of the patients were found to have heartburn, and 39% of the patients said they had had vomiting fits. The other two most prevalent complaints were pain (35%) and flatulent dyspepsia (47%) [15].

Haemoglobin levels in the control and H. pylori groups were statistically substantially greater than those in the cancer group in the current investigation. Regarding the platelet count, there was no statistically significant difference. In comparison to the H. pylori group, the WBC count in the cancer group was statistically considerably greater. Statistically significant differences were seen in the creatinine level between the H. pylori group and the control group and the cancer group. Hou et al reported that anemia was more common in the H. pylori positive group (5.3% vs. 2.2%, P =0.033) than in the negative group overall. They also reported that no correlation between H. pylori infection and serum iron and ferritin levels was found [16].

Endoscopic findings in the research groups showed that there were no cases of gastritis, sliding HH, or GERD in the control group. When compared to the cancer group, the H. Pylori group had a statistically significant greater incidence of sliding HH.

According to Manes et al.'s study, group A had an overall hernia prevalence of 11%, group B had a prevalence of 23%, and group C had a prevalence of 38%. The prevalence of H. pylori infection increased significantly with ageing, and it was higher in patients without GERD than in those with GERD (66.4 vs. 57.3%, $P < 0.05$) [17].

Our research indicates that nodularity was non-existent in both the cancer and control groups. When compared to other groups, the cancer group's PDL1 Tumour Proportion score, Combined Positive Score and inflammatory cell expression were all statistically substantially higher. Additionally, the H. pylori group's Combined positive score was statistically considerably greater than the control groups.

Similar to our results, Holokai et al. first obtained gastric biopsies from uninfected normal subjects and infected patients who showed metaplasia in order to ascertain if H. pylori causes PD-L1 expression in the stomach. In contrast to the typical control group of patients, It was discovered that the presence of H. pylori infection increased the expression of PD-L1. Furthermore, 48 hours after infection, H. pylori dramatically elevated PD-L1 expression in organoid cells relative to uninfected controls [6].

Aydın et al., also examined the mRNA expression of PD-1 and PD-L1 in patients with gastritis (n = 36), gastric ulcers (n = 21), and gastric cancer (n = 14). It was demonstrated that

patients with gastric ulcers (PD-1: 2.3 fold, p=0.01; PD-L1: 2.1 fold, p=0.004) and gastric cancer (PD-1: 2 fold, p= 0.04; PD-L1: 1.8 fold, p=0.05) had higher levels of PD-1 and PD-L1 mRNA expressions in their stomach tissue as compared to control participants [18].

Zheng et al.'s approach to assess the relationship between prognosis and circulating PD-L1 expression in patients with advanced gastric cancer is in line with our findings. The study included 40 healthy controls and 80 patients with advanced stomach cancer. When comparing advanced gastric cancer patients to healthy individuals, there was a significant up-regulation of PD-L1 expression (P=0.006) [19].

The endoscopic results showed no statistically significant variation in the PDL-1 level, with the exception that the cases with gastritis had a statistically significant increase in PDL-1 level. The pathology data indicated that there was no statistically significant difference in the PDL-1 level.

There is a strong correlation between advanced clinicopathological characteristics and poor mortality in GC patients with PD-L1 expression. Further highlighting the significance of PD-L1 expression on GC biology and its potential as a molecular target for advanced-stage GC treatment, a single nucleotide polymorphism at the PD-L1 miR-570 binding region was linked to an elevated risk for the development of GC [20].

Pathological characteristics such as reduced differentiation grade, depth of invasion, lymph node metastasis, and TNM stage were substantially and favorably correlated with PD-L1 overexpression in GC, which was caused by a guanine-to-cytosine mutation in the 3'-UTR of PD-L1 mRNA [21].

The PDL-1 level in the H. pylori group did not differ statistically significantly based on the severity of the disease in the current investigation. The histopathological results in the cancer group showed no statistically significant variation in the PDL-1 level. Based on pathological findings, there was no statistically significant variation in the severity of the disease in the H. Pylori group.

Hou J. et al. discovered a positive correlation between PD-L1 overexpression in GC and an increase in the Treg cell population. These variables were linked to an increased risk of lymph node metastasis, an advanced clinicopathological stage, and a worse overall survival rate 17) [22].

PD-L1 did not, however, connect with tumour stage, depth of invasion, differentiation, or location of the cancer. According to meta-analysis by Zhang et al in 2016, PD-L1 expression is a useful indicator of how well gastric cancer patients would fare [23].

CONCLUSION

According to our research, stomach cancer and H. pylori-associated gastritis may benefit from the existence of gastric mucosal nodularity and programmed death ligand 1 (PD-L1) expression as potential prognostic indicators. These markers may be important for early diagnosis and treatment of these disorders, potentially leading to better patient outcomes. This is demonstrated by the observed correlations between these markers and different clinical and histological criteria .

Author contribution: We declare that all listed authors have made substantial contributions to all the following three parts of the manuscript:

-Research design, or acquisition, analysis or interpretation of data.

-Drafting the paper or revising it critically.

-Approving the submitted version.

We also declare that no-one who qualifies for authorship has been excluded from the list of authors.

Ethical considerations:

The study is approved by the ethics committee of National Liver Institute, Menoufia University (IRB number: 00535/2024) and conducted in accordance with Helsinki standards.

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Conflict of interest: NoneTable1: Annual prevalence of yeast cases

RESEARCH HIGHLIGHTS:

- Chronic gastritis is linked to *H. pylori* and it is also linked to atrophy, metaplasia, dysplasia and malignancy.
- Although the exact process is uncertain, *H. pylori* also causes gastric epithelial cells to express programmed death ligand 1 (PD-L1.(

- PD-L1 expression and an endoscopic nodule-like appearance could identify stomach cancer and *H. pylori*-associated gastritis

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