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RESEARCH ARTICLE

Helicobacter pylori in primary gastric lymphoma and gastric cancer: A clinicopathologic and prognostic assessment

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ABSTRACT

Objectives: *Helicobacter pylori* infection is a risk factor for gastric adenocarcinoma and primary gastric lymphoma. We examined whether this *H. pylori* infection is also a prognostic factor for gastric cancer and primary gastric lymphoma.

Methods: Resected or biopsied specimens from 255 patients with gastric adenocarcinoma and primary gastric lymphoma were investigated for *H. pylori* status. Hematoxylin and eosin stain was used to evaluate the presence or absence of *H. pylori* on formalin fixed, paraffin embedded specimens.

Results: *H. pylori* were detected in 34 of 140 patients (24.3%) with primary gastric lymphoma, while *H. pylori* were detected in 62 of 115 patients (53.9%) with gastric cancer. The frequency of *H. pylori* positivity was higher in patients with gastric cancer than in those with gastric lymphoma (p<0.001). The frequency of *H. pylori* positivity was different between mucosa-associated lymphoid tissue type (MALT) lymphomas (53.5%) and lymphomas other than diffuse large b-cell lymphoma (DLBCL) (18.7%) in gastric lymphoma (p<0.001). For patients with primary gastric lymphoma, *H. pylori* status did not correlate with the disease free survival and overall survival (p=0.833, p= 0.503). However for patients with gastric cancer, *H. pylori* status did not correlate with the disease- free survival and overall survival (p=0.392, p= 0.357).

Conclusions: In our study, between gastric cancer and primary gastric lymphoma were significant differences in terms of the presence of H. pylori. However, *H. pylori* did not have prognostic significance on survival for both pairs. *J Microbiol Infect Dis 2013; 3(2): 61-66*

Key words: *H. pylori*, primary gastric lymphoma, gastric cancer

Primer mide lenfoma ve mide kanserinde Helikobakter pylori: Klinik-patolojik ve prognoztik değerlendirme

ÖZET

Amaç: Helicobacter pylori mide lenfoması ve adenokarsinom için risk faktörüdür. Bu çalışmada *H. pylori*'nin primer mide lenfoma ve mide kanserinde prognostik faktör olup olmadığı incelendi.

Yöntemler: Primer mide lenfoma ve mide kanserli 255 hastanın rezeksiyon veya biyopsi materyalleri *H. pylori* açısından incelendi. Patoloji spesmenlerinde *H. pylori* varlığını değerlendirmek için hematoksilen ve eozin boyası kullanıldı.

Bulgular: Primer mide lenfomalı 140 hastanın 34'ünde (%24,3) *H. pylori* saptanırken mide kanserli 115 hastanın 62'sinde (%53,9) *H. pylori* saptandı. *H. pylori* varlığı mide kanserli hastalarda, mide lenfomalardan daha sık görüldü (p<0.001). *H. pylori* pozitifliği, mide lenfoma içinde mukoza ilişkili lenfoid doku tip lenfomada (MALT) %53,5 oranında, diffüz büyük B hücreli lenfomadan farklı olarak %18,7 oranında görüldü (p<0,001). Primer mide lenfoma da *H. pylori*'nin varlığı hastalıksız sağkalım ve genel sağkalım açısından anlamlılık oluşturmuyordu (p=0,833, p= 0,503). Bununla beraber mide kanserli hastalarda da *H. pylori* varlığı ile hastalıksız sağkalım ve genel sağkalımda da anlamlılık oluşturmuyordu (p=0,392, p= 0,357).

Sonuç: Çalışmamızda mide kanserli ve primer mide lenfoma arasında *H. pylori* varlığı bakımından anlamlı farklılık vardı. Ancak *H. pylori* varlığı, hem hastalıksız sağkalım hem de genel sağkalım açısından prognostik anlamlılık oluşturmuyordu.

Anahtar kelimeler: *H. pylori*, Primer mide lenfoma, Mide kanser

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INTRODUCTION

Helicobacter pylori infection colonizes the stomach of more than half of the world's population, and it has been believed to play a decisive role in such gastroduodenal diseases as chronic active gastritis, peptic ulcer, and gastric carcinoma and primary gastric lymphoma, especially the lymphoma of mucosa-associated lymphoid tissue (MALT) type.[1-3] In 1994 the International Agency for Research on Cancer World Health Organization classified *H. pylori* as group 1 recognized human carcinogen.[4] Studies have also reported that low grade gastric MALT lymphoma and gastric cancer may regress after the eradication of *H. pylori*. Several studies have demonstrated a reduction of the risk of gastric cancer after *H. pylori* eradication.[5-7] Infection with *H. pylori* is implicated in the pathogenesis and treatment of gastric MALT lymphoma, but the role of *H. pylori* in gastric Diffuse Large B-Cell Lymphoma (DLBCL) is uncertain .[8-9]

Gastric cancer is the fourth most common type of cancer and the second most common cause of cancer-related mortality around the world.[10] Lauren described the two histological types of gastric cancer as the intestinal and the diffuse types.[11] After the initiation by *H. pylori* and the influence of variable environmental and host factors, chronic active gastritis may progressively evolve to atrophic gastritis and intestinal metaplasia. In some individuals the metaplastic epithelium will undergo further genomic and phenotypic changes, resulting in gastric dysplasia and finally ending in adenocarcinoma.[12]

In the current study, we investigated 255 patients with primary gastric lymphoma and gastric carcinoma to detect the prognostic role of *H. pylori*. The aim of this study was to determine the pattern of histologically-proven gastric cancer and lymphoma and explore its association with *H. pylori* infection.

METHODS

For the purposes of this study, the medical records of the patients treated at five Medical Centers in Turkey between 2005 and 2010 were retrospectively evaluated. The inclusion criteria were a histologically confirmed adenocarcinoma of the stomach or primary gastric lymphoma. Approving for this study was taken by the ethics committee. We obtained written informed consent from all participants, *H. pylori* status was performed by histological in the surgical specimens. Hematoxylin and eosin stain was used to evaluate the presence or absence of *H. pylori* on formalin fixed, paraffin embedded specimens.[13] We defined a positive result for *H. pylori* infection as when the histological result was positive. Pathologic results were recorded, including the tumor size, location, and type, according to the Lauren and WHO histological classifications. A histologic classification of the primary gastric lymphoma specimens was performed according to the criteria of Isaacson et al.[14] Disease stage was designated in all patients according to the Lugano staging system for gastrointestinal non-Hodgkin's lymphoma.[15] Disease stage was performed according to the guidelines of the American Joint Committee on Cancer (AJCC) (6th and 7th edition) for gastric cancer.[16] All patients in this study were assessed for the recurrence of gastric cancer and death every three to six months through the use of computed tomography, tumor marker expression and physical examination. A chi-squared test was used to analyze correlations between the clinicopathologic features and *H. pylori* status. Overall and disease-free survival and *H. pylori* status were analysed using the Kaplan-Meier test. Statistical analyses were performed using SPSS 18.0 for Windows, and p values <0.05 were considered statistically significant.

RESULTS

A total of 115 cases of gastric cancer and 140 cases of primary gastric lymphoma were diagnosed. The median age of the all patients was 58 years (range=18-85 years). There were 152 males (59.6%) and 103 females (40.4%) with a male to female ratio of 1.4-1. Characteristics of the all patients are summarized in Table 1. According to the AJCC staging system of the patients of gastric cancer (n=105), 67 (63.8%) were at stage I-II, while 28 (36.2%) were at stage III- IV. According to the Lauren classification, 47 (58.0%) patients had the intestinal type of gastric cancer and 34 (42.0%) had the diffuse type. In the examining of 115 patients with gastric cancer in term of *H. pylori* infection, 62 (53.9%) of the patients were positive and 53 (46.1%) of the patients were negative (p<0.001) (Table 2). Among the patients who were positive in terms of *H. pylori* infection, 32 (62.7%) had the intestinal type of gastric cancer, while 19 (37.3%) had the diffuse type. *H. pylori* infection was more frequent in intestinal adenocarcinoma than in diffuse adenocarcinoma. Moreover the patients who were negative in terms of *H. pylori* infection, 15 (50.0%) had the intestinal type of gastric cancer, while 15 (50.0%) had the diffuse type (p=0.262). Among the patients who were positive in terms of *H. pylori* infection, 29 (55.8%) had the distal type of gastric cancer, while 23 (44.2%) had the proximal type. Moreover the patients who were negative in terms of *H. pylori* infection, 14 (45.2) had the

distal type of gastric cancer, while 17 (54.8%) had the diffuse type (p=0.349). The survival analysis was based on patients with gastric cancer (Table 2). The median follow-up period was 18.2 months (range: 2.2-93.4 months). The Overall Survival (OS) rates were 84%, 52%, and 38%; while the Disease free survival (DFS) rates were 84%, 61%, and 49% at 1, 3 and 5-years, respectively. In the median follow-up period, relapse was observed in 29 patients (25.2%) and 37 (32.1%) among them died. The 3-year DFS rate was 66% for the *H. pylori* positive with gastric cancer cases, whereas it was 56% for the *H. pylori*-negative cases (p=0.392); however, The 3-year OS rate was 63.8% for the *H. pylori*-positive with gastric cancer cases, whereas it was 49.5% for the *H. pylori*-negative cases (p=0.357) (Figure 1).

Table 1. Characteristics of the patients.

	Primary Gastric Lymphoma				Gastric Cancer		
	HP (+)	HP(-)	P value		HP (+)	HP (-)	P value
Sex (n)	34	106			62	53	
Male n (%)	17 (50.0)	53 (50.0)	1.0		44 (71.0)	38 (71.7)	0.931
Female	17 (50.0)	53 (50.0)			18 (29.0)	15 (28.3)	
Histology (n)	33	91		Histology	51	30	
DLBCL n (%)	18 (54.5)	78 (85.7)	<0.001	Diffuse	19 (37.3)	15 (50.0)	0.262
MALT	15 (45.5)	13 (14.3)		Intestinal	32 (62.7)	15 (50.0)	
Grade (n)	16	44			56	37	
Low-interm n(%)	7 (43.7)	19 (43.2)	0.969		26 (46.4)	19 (51.4)	0.642
High	9 (56.3)	25 (56.8)			30 (53.6)	18 (48.6)	
Stage (n)	30	104			55	40	
Stage I-II n (%)	24 (80.0)	70 (67.3)	0.181		18 (32.7)	10 (25.0)	0.415
Stage III-IV	6 (20.0)	34 (32.7)			37 (67.3)	30 (75.0)	
Localization (n)	25	82			52	31	
Proximal n (%)	16 (64.0)	50 (61.0)	0.785		23 (44.2)	17 (54.8)	0.349
Distal	9 (36.0)	32 (39.0)			29 (55.8)	14 (45.2)	

HP=*Helicobacter pylori*.

Table 2. Comparison of Primary Gastric Lymphoma and Gastric cancer.

Criteria	Primary Gastric Lymphoma			Gastric cancer		
	HP (+)	HP (-)	P value	HP (+)	HP (-)	P value
N (%)	34 (24.3)	106 (75.7)		62 (53.9)	53 (46.1)	<0.001
3 years Survival DFS (%)	82.4	78.0	0.833	66.0	56.0	0.392
3 years Survival OS (%)	73.5	65.3	0.503	63.8	49.5	0.357

HP=*Helicobacter pylori*, DFS=Disease-free survival, OS=Overall survival.

The overall frequency of *H. pylori* infection in primary gastric lymphoma cases was 23% (34/140). The frequency of *H. pylori* positivity was differ between MALT lymphomas (53.5%) and lymphomas other than DLBCL (18.7%) (p<0.001). The proximal stomach (corpus and fundus) was the most commonly involved area within the stomach site (66 cases, 61%) in our study, followed by the distal stomach (antrum, pylor) (41 cases, 39%). *H. pylori* positivity was less frequent for the distal gastric localization (21.2%) than for the proximal gastric (24.2%). No statistically significant relationship was not observed between the tumor localization and the *H. pylori* status (p=0.785). Among the gastric lymphomas, the frequency of *H. pylori* positivity was not significantly for low-grade tumors (26.9%) and for high-grade tumors (26.4%) (p=0.969). The presence of *H. pylori* did not correlate with patients' sex, or disease stage; positivity was 25.5% for Stage I-II, 15% for Stage III-IV (p=0.181). Median follow-up time was 23.9 months (range 1.2-200.0 months) and 3-5 year OS rates were 67.4% and 63.9%. The 3-5 year DFS

rates were 79.2% and 74.2%. 38 (27.1%) patients died while 24 (17.1%) of the patients relapsed. The 3-year and 5-year overall survival rates were 73.5% and 82.4% for the *H. pylori*-positive with primary gastric lymphoma cases, whereas they were 65.3% and 60.7% for the *H. pylori*-negative cases, respectively (p=0.503) (Figure 2); however, the 3-year and 5-year DFS rates were 82.4% and 82.4% for the *H. pylori*-positive with primary gastric lymphoma cases, whereas they were 78.0% and 71.5% for the *H. pylori*-negative cases, respectively (p=0.833) (Table 2). For patients with primary gastric lymphoma, *H. pylori* status did not correlate with the DFS and OS.

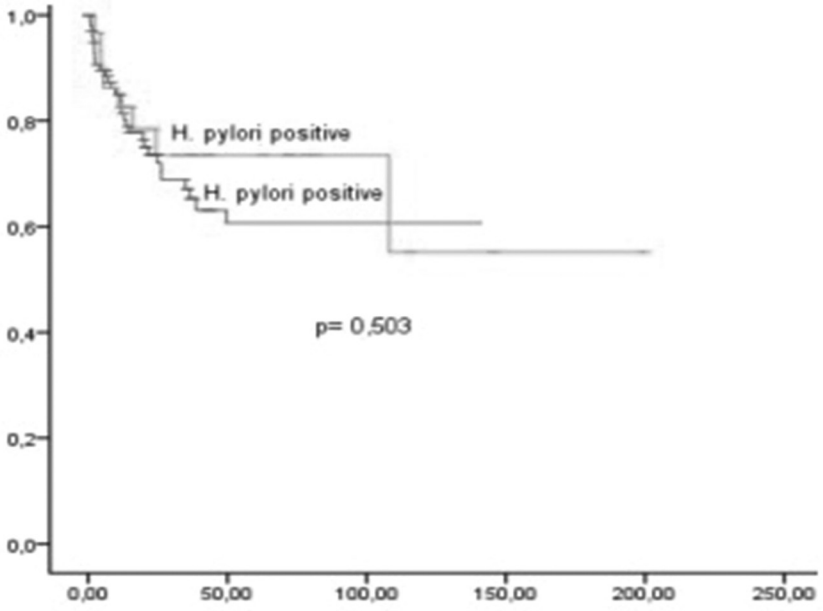

Figure 1. Comparison of overall survival curves of patients with gastric cancer with *H. pylori*-positive and negative.

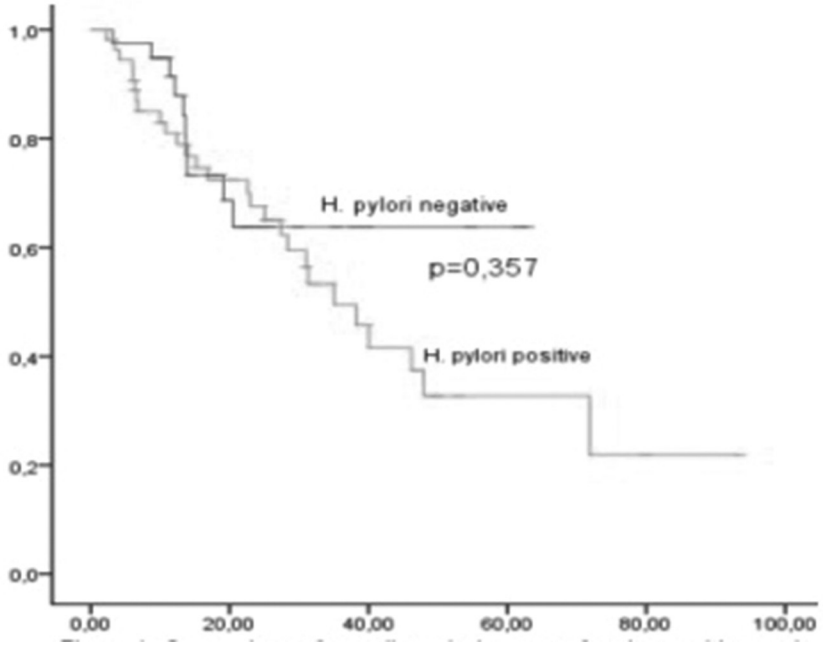

Figure 2. Comparison of overall survival curves of patients with gastric lymphoma with *H. pylori*-positive and negative.

DISCUSSION

Helicobacter pylori infection remains common worldwide and is significantly associated with gastric adenocarcinoma and gastric MALT lymphoma.[17] Between gastric cancer and primary gastric lymphoma were significant differences in terms of the presence of *H. pylori*. There was a higher rate of *H.*

pylori positivity in patients with gastric cancer. More significant correlation was found between gastric cancer and *H. pylori* status. No statistically significant relationship was observed between the tumor localization and the patients' sex, Lauren classification and *H. pylori* status in our study. Several studies have described a high prevalence of *H. pylori* infection in gastric lymphoma.[3,18]

Epidemiological studies have demonstrated a significant correlation between *H. pylori* infection and gastric cancer, indicating that *H. pylori* infection may be involved in approximately 35-60% of gastric cancer cases.[1,19] In our study, *H. pylori* positivity was significantly lower than in other studies that used serologic test. It may be due to no serologic tests were available in our study. Some recent studies have described the regression of low grade gastric MALT lymphoma after the eradication of *H. pylori*.[20,21] In our region, the high rate *H. pylori* positivity (57.1%) in stomach cancer was also seen in previous studies.[22] For this reason, *H. pylori* eradication may be the strategy in the patients with gastric cancer. The strategy of test, treat and screening for *H. pylori* infection is effective in reducing the incidence and mortality of gastric cancer in communities with a high incidence of gastric cancer. The risk of non-cardia gastric cancer was about six times higher in those who tested positive for *H. pylori*. *H. pylori* infection was detected more frequently in the intestinal type of tumor and distal gastric cancer. In the study conducted on a Turkish population, positive *H. pylori* tests were more common in patients with distal gastric cancer and intestinal type of tumor; and the difference was found as statistically significant.[23] Epidemiological studies suggest a strong association between *H. pylori* infection and distal gastric cancer. One estimate attributed 70% of non-cardiac gastric adenocarcinoma to *H. pylori* infection.[24]

Overall 5-year survival between 50% and 70% is reported with multimodality therapy for gastric lymphoma.[25] The prognosis of gastric cancer continues to be poor, with a 5-year survival rate of approximately 20% except for a few countries (e.g. 40%-60% in Japan).[26] In this study, survival rates were similar in the cases of gastric cancer and lymphoma. The most important prognostic factor for gastric cancer and lymphoma patients is tumor-node-metastasis (TNM) stage. The prognostic significance of *H. pylori*, which is an important predisposing factor in the pathogenesis of gastric malignancies, have evaluated in very few studies. In performed a study, a negative *H. pylori* status may be a predictive factor for recurrence in patients diagnosed with advanced gastric adenocarcinoma.[27] In other study, negative *H. pylori* status appears to be an indicator of poor prognosis in patients with gastric cancer, and is independent of other well-known clinical and pathologic prognostic variables.[28] *H pylori* was an independent prognostic factor for DFS and OS. *H. pylori* positive patients had a significantly better survival.[29]

In conclusion, *H. pylori* status did not correlate with the clinicopathologic factors of gastric adenocarcinoma and primary gastric lymphoma in our study. There was no correlation between *H. pylori* status and stage in this study.

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