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Original Article

Relationship Between *Helicobacter Pylori* and Intestinal Metaplasia: A Rural Hospital Experience

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ABSTRACT

Objective: *Helicobacter pylori* (Hp) is a risk factor for gastric cancer, and intestinal metaplasia (IM) is one of the precursor lesions of gastric cancer. The aim of this study was to examine the relationship between Hp and IM.

Methods: A total of 550 patients who underwent upper gastrointestinal endoscopy between October 2018 and December 2019 were included in the study. The patient data of age, sex, endoscopic diagnosis, Hp positivity, IM, atrophic gastritis, and neoplasia were evaluated retrospectively.

Results: There were 550 patients enrolled in the study: 228 males (41.5%) and 322 females (59.5%), with a median age of 37.0 years (interquartile range: 18.0–79.0 years). Hp was detected in 62.7% of the patients, IM in 17.1%, gastric atrophy in 9.1%, and gastric cancer in 2.9%. Among the patients with positive IM, 80 were Hp-positive and 14 were Hp-negative. The rate of IM was significantly higher in Hp-positive patients than in Hp-negative patients ($p<0.001$). In addition, the incidence of Hp-IM coexistence was significantly higher in patients over 50 years of age ($p=0.002$).

Conclusion: There was a strong relationship between Hp and IM, and the relationship was correlated with age. Hp eradication is critical to prevent the development of IM, a precursor lesion of intestinal-type gastric cancer.

INTRODUCTION

Helicobacter pylori (Hp), is a small (0.5–3 μm), Gram-negative, spiral-shaped, curved, and motile bacterium with 4 to 6 flagella. It grows in a microaerophilic 37°C environment and is urease-, catalase-, and oxidase-positive. It is genetically highly polymorphic due to the development of point mutations, but the biochemical characteristics do not change. Since its discovery and isolation by Warren and Marshall, Hp has been associated with the etiology of numerous gastrointestinal (GI) diseases, such as chronic gastritis, peptic ulcer, gastric cancer, mucosa-associated lymphoid tissue lymphoma, and biliary tract cancer.[1–4]

The development of gastric cancer is a multistep process of changes in the gastric mucosa, beginning as non-atrophic gastritis or atrophic gastritis, and potentially developing into intestinal metaplasia (IM), dysplasia, and finally carcinoma.[5] This process is thought to be initiated and promoted by Hp.[6] Hp targets cellular components by using various virulence factors to modulate host proliferation, apoptosis, migration, and the inflammatory response.[7] As a result, this bacterium has been classified by the International Agency for Research on Cancer of the World Health Organization as a class I carcinogen.[8] The discovery of Hp dramatically changed the image of gastric cancer from a devastating cryptogenic disease to one that is infectious and preventable.[9] The diagnosis and eradication of Hp play a vital role in stopping the process that leads to the development of gastric cancer.

The objective of this study was to investigate the frequency and the association of Hp and IM in Hakkari province, Turkey.

MATERIALS AND METHODS

This retrospective study was conducted in the endoscopy unit of the Hakkari State Hospital general surgery department. The Yüzüncü Yıl University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study on January 29, 2020 (no: 03). The records of 550 patients who had undergone upper GI endoscopy between October 2018 and December 2019 were included in the study. Patients with known upper GI malignancy or surgery, those under the age of 18, and those who had endoscopy for GI bleeding were excluded from the study. The data were obtained from the endoscopy and pathology reports and discharge forms. The patients were evaluated in terms of age, gender, endoscopic diagnosis, Hp positivity, atrophic gastritis, IM, and neoplasia. Patient confidentiality was preserved.

All of the endoscopic procedures were performed using a Pentax FG-32X gastroscope (Pentax Medical, Tokyo, Japan). Endoscopic biopsies were obtained from 5 regions of the stomach in accordance with the Sydney protocol.[10] After routine tissue processing of the endoscopic biopsy material, hematoxylin-eosin was applied and Giemsa and Alcian blue stains were used to detect the presence of IM, Hp positivity, gastric atrophy, and neoplasia.

The categorical data were described using number and percentage values, while continuous data were presented with the interquartile range (IQR) (25^{th}–75^{th} percentile). Chi-squared and Fisher tests were used to compare categorical data. The Kolmogorov-Smirnov test was applied to evaluate normal distribution. The Mann-Whitney U test was used to compare non-parametric variables between groups, and binary logistic regression was used for correlation analysis. A p value of <0.05 was considered statistically significant for all of the analyses. IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis.

RESULTS

Of the 550 patients enrolled in the study, 228 were male (41.5%) and 322 were female (59.5%), and the median age was 37.0 years (IQR: 18.0-79.0 years). Hp was detected in 62.7% of the patients, IM in 17.1%, gastric atrophy in 9.1%, and gastric cancer in 2.9% (Table 1). The rates of IM and gastric cancer were significantly higher in male patients than female patients (p=0.038 and p=0.006, respectively). There was no significant difference between male and female patients in terms of Hp positivity or gastric atrophy (Table 2). Of the patients with positive IM, 80 were Hp-positive and 14 were Hp-negative. The IM rate was significantly higher in the Hp-positive patients than in the Hp-negative patients (p<0.001). The gastric atrophy and neoplasia rates were significantly lower in the Hp-positive patients (p<0.001) (Table 3).

Table 1. The pathological diagnosis of the patients

		n	%
Helicobacter pylori	Positive	345	62.7
	Negative	205	37.3
Intestinal metaplasia	Positive	94	17.1
	Negative	456	82.9
Gastric atrophy	Positive	50	9.1
	Negative	500	90.9
Gastric cancer	Positive	16	2.9
	Negative	534	97.1

Table 2. Pathological diagnosis of the patients by gender

	Gender				p
	Male		Female		
	n	%	n	%	
Helicobacter pylori					
Positive	134	58.8	211	65.5	0.106[a]
Negative	94	41.2	111	34.5	
Intestinal metaplasia					
Positive	48	21.1	46	14.3	0.038[a]
Negative	180	78.9	276	85.7	
Gastric atrophy					
Positive	23	10.1	27	8.4	0.494[a]
Negative	205	89.9	295	91.6	
Gastric cancer					
Positive	12	5.3	4	1.2	0.006[b]
Negative	216	94.7	318	98.8	

[a]Chi-squared test; [b]Fisher's exact test.

Table 3. Other pathological findings according to *Helicobacter pylori* result

	Helicobacter pylori				p
	Positive		Negative		
	n	%	n	%	
Intestinal metaplasia					
Positive	80	23.2	14	6.8	<0.001[a]
Negative	265	76.8	191	93.2	
Gastric atrophy					
Positive	20	5.8	30	14.6	<0.001[a]
Negative	325	94.2	175	85.4	
Gastric cancer					
Positive	2	0.6	14	6.9	<0.001[b]
Negative	343	99.4	189	93.1	

[a]Chi-squared test; [b]Fisher's exact test.

There was a significant relationship between age and the finding of IM. The mean age of IM-positive patients (45.31±15.73 years) was greater than that of the IM-negative patients (40.07±15.98 years) (p=0.002). The effect of age on the presence of IM was examined using binary logistic regression, and it was determined that each unit of increase in age increased the risk of IM 1.02 times (p=0.004) (95% confidence interval: 1.006–1.033). The coexistence of Hp and IM was significantly greater in patients over 50 years of age when compared with patients under 50 (p=0.002).

DISCUSSION

There are 3 potential mechanisms thought to be responsible for Hp-related gastric damage: local tissue damage caused by increased toxic products, induction of a local mucosal immune response, and increased acid secretion due to an increased gastrin level.[2] The chronic inflammation caused by Hp produces histopathological changes in the gastric epithelium, which leads to the continuous production of cytokines. The cytokines stimulate the release of oxidative radicals, which damage the host DNA.[6] Over time, superficial gastritis that starts in the antrum spreads to the entire stomach (pangastritis) and the inflammation deepens and becomes full-thickness mucosal gastritis. This progressive process may lead to more serious histopathological changes, such as atrophy, IM, and dysplasia, and thus, Hp is considered a risk factor for gastric cancer.[11,12] It has been reported in meta-analyses that the gastric cancer risk is 2- to 3-fold greater in Hp-positive patients, while it is 6.4-fold greater in Hp-positive IM patients.[13–15] Recent systematic reviews and meta-analyses have demonstrated a reduction in primary and metachronous gastric cancer with Hp eradication.[16,17]

More than 50% of the world's population is infected with Hp. An incidence of 30% has been reported in the USA, while it was 70% in eastern Europe, and 70% to 80% in Asia.[18] The rate of Hp infection is higher in societies that are poor, socioeconomically underdeveloped, lack healthy nutrition, and have inadequate sanitation. The prevalence of Hp in Turkey is similar to that of developing countries, but the results of epidemiological studies are contradictory in our country due to varied study methods and a diverse prevalence by region. The most comprehensive study of the epidemiology of Hp in adults in Turkey was conducted by Ozaydin et al.[19] in 2003. A 13C-urea breath test was used and the overall prevalence of Hp was determined to be 82.5% in 5549 adults, with a male prevalence of 84% and a female prevalence of 81%. In the same study, the prevalence of Hp was highest (88%) in those living in the Eastern Anatolia region and lowest (79%) in those living in the Southeastern Anatolia region.

Ozden et al.[20] reported a prevalence of Hp antibodies across Turkey of 78.5% in 1990, while it was 66.3% in 2000. Çiftel et al.[21] noted an Hp rate in the Erzurum region of 57% and Şermet et al.[22] found that the rate was 87% in the Şanlıurfa region. Our study was unable to determine a Hp prevalence since we did not use a cross-sectional design. However, the frequency (incidence) of Hp in patients who visited our clinic is 62.7%.

The relationship between Hp and IM is controversial. Some researchers consider IM to be a sequela of inflammation and part of the progressive process, while others have suggested that the cause of IM may be exogenous and/or dietary factors rather than Hp. Asaka et al.[23] investigated the relationship between Hp and atrophic gastritis and IM. The rate of atrophic gastritis was 82.9% in the Hp-infected group, while it was 9.8% in the non-infected group. Similarly, the frequency of IM was 43.1% in the infected group and 6.2% in the non-infected group. Craanen et al.[24] reported that IM was more common in Hp-positive cases than in Hp-negative cases. Ohkuma et al.[12] observed that both aging and Hp were involved in the development of IM. The decreased frequency of IM in Hp-eradicated patients supports a strong relationship between Hp and IM.[25] Our results also indicated a strong association between Hp and IM.

In the literature, the relationship between Hp and IM has been shown to correlate with age and increase significantly after the age of 50.[24] Asaka et al.[23] reported that the prevalence of IM in Hp-positive patients below 30 years of age was 8.9%, while it was 57% in those older than 60.[23] In our study, we observed that the risk of developing IM increased 1.02 times with each year of age and that the relationship between Hp and IM increased significantly after the age of 50.

Given this significant relationship between Hp and IM, individuals with a high risk for gastric cancer and Hp-positive patients should be advised and educated about the need to perform endoscopic follow-up. Woo et al.[26] observed an association between IM and recent Hp biopsy results, but noted that previous Hp results should not be considered a reliable criterion for gastric cancer screening and follow-up. A gastric cancer surveillance program according to risk stratification should be established after Hp eradication. Shichijo and Hirata[27] reported that following eradication, depressed-type gastric cancer can be seen endoscopically and has a gastritis-like appearance. Histologically, intestinal-type gastric cancer and an epithelium with low-grade atypia are most common after Hp eradication. Molecular markers, such as Ki67, MUC2, and Wnt5a expression, are lower in Hp-eradicated cancer patients. While atrophic gastritis may regress with Hp eradication, the presence of IM may be a point of no return in this cascade. Hence, endoscopy surveillance is indicated in those with extensive IM as well as those with incomplete IM, particularly in populations with a high gastric cancer risk.[28] The optimal interval and the best tool for surveillance endoscopy remains unclear.

To the best of our knowledge, our study is the first in the literature to report the frequency of Hp and IM in Hakkari province. This is a useful contribution; however, our study had some limitations, principally due to the fact that it

was retrospective research from a single center, included a small number of patients, and no cross-sectional screening was performed.

CONCLUSION

The results of our study demonstrated a strong relationship between Hp and IM, and this relationship was correlated with increasing age. Hp eradication is critical to prevent the development of IM, which is a precursor lesion of intestinal-type gastric cancer.

Ethics Committee Approval

The Yüzüncü Yıl University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study on January 29, 2020 (no: 03).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: O.A., E.Ç.; Design: O.A., Ö.G.; Supervision: S.E., S.M.A.A.; Materials: O.A., E.Ç.; Data: Ö.G., E.Ç.; Analysis: O.A., Ö.G.; Literature search: O.A., S.E., S.M.A.A.; Writing: O.A.; Critical revision: S.E., S.M.A.A.

Conflict of Interest

None declared.

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Helicobacter pylori ve İntestinal Metaplazi İlişkisi: Kırsal Bir Hastane Deneyimi

Amaç: Helicobacter pylori (Hp) gastrik kanser için bir risk faktörü iken intestinal metaplazi de gastrik kanserin prekürsör lezyonlarından bir tanesidir. Bu çalışmada Hp ile intestinal metaplazi arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Ekim 2018–Kasım 2019 tarihleri arasında üst gastrointestinal endoskopisi yapılan toplam 550 hasta çalışmaya dahil edildi. Hastalar yaş, cinsiyet, endoskopik tani, Hp pozitifliği, intestinal metaplazi, gastrik atrofi ve gastrik kanser açısından geriye dönük olarak değerlendirildi.

Bulgular: Çalışmadaki 550 hastanın 228'i erkek (%41.5), 322'si kadındı (%59.5) ve ortanca yaş 37.0 idi (18.0–79.0). Hastaların %62.7'sinde Hp, %17.1'inde intestinal metaplazi, %9.1'inde gastrik atrofi ve %2.9'unda gastrik kanser görüldü. İntestinal metaplazi pozitif hastaların 80'inde Hp pozitif, 14'ünde ise Hp negatif saptandı. Hp pozitif hastalarda intestinal metaplazi görülme oranı, Hp negatif hastalara göre anlamlı derecede daha yüksekti ($p<0.001$). Ayrıca Hp - intestinal metaplazi birlikteliğinin 50 yaş üstü olgularda 50 yaş altı olgulara göre anlamlı derecede daha fazla olduğu görüldü ($p=0.002$).

Sonuç: Helicobacter pylori ile intestinal metaplazi arasında kuvvetli bir ilişki mevcuttur ve bu ilişki yaş ile koreledir. İntestinal tip gastrik kanserin prekürsör lezyonu olan intestinal metaplazinin gelişimini önlemede Hp eradikasyonu kritik öneme sahiptir.

Anahtar Sözcükler: Endoskopi; Helicobacter pylori; intestinal metaplazi.