Is gastric intestinal metaplasia a risk factor for colorectal neoplasms?

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ABSTRACT
Colorectal cancers are one of the most common types of cancer. Gastric intestinal metaplasia is considered a precancerous lesion that can progress into gastric cancer. Even though there are previous reports that Helicobacter pylori and intestinal metaplasia are related to colorectal adenomas, there are also studies stating the opposite. This study aimed to explore the relationship between gastric intestinal metaplasia and colorectal neoplasia. A total of 214 patients between the ages of 19 and 92 who underwent combined gastroscopy and colonoscopy between August 2016 and April 2020 were included in this retrospective study. Medical records including demographic data, gastroscopy and colonoscopy findings and histopathology results of the patients were reviewed and analyzed. The association of intestinal metaplasia and H. pylori infection with colorectal neoplasia was evaluated in these patients. The mean age of the patients included in the study was 49.07 ± 15.80, and 125 (58.4%) of the patients were male. A statistically significant correlation was found between intestinal metaplasia and colon neoplasm prevalence (p = 0.03). However, such a correlation was not seen between H. pylori and colon neoplasia. In conclusion, a positive correlation was found between gastric intestinal metaplasia, which is a precancerous lesion, and colon neoplasia. Even though this correlation indicates higher prevalence rates of colon neoplasia in patients with gastric intestinal metaplasia, how to evaluate these patients in terms of colon neoplasia remains a controversial issue.

Introduction
Gastric cancer, which has a gradually decreasing incidence in many industrialized countries, still remains the second leading cause of cancer related deaths around the world [1]. Gastric cancer is classified into two main types: intestinal and diffuse. Intestinal type gastric cancer is related to premalignant lesions such as chronic atrophic gastritis (AG) and intestinal metaplasia (IM) [2, 3]. IM, defined as gastric mucosa changing into epithelium with intestinal morphology, is associated with Helicobacter pylori (H. pylori) infection, and during this infection, gastric mucosa progresses into many stages of chronic gastritis, AG and IM [4, 5].

Colorectal cancers (CRC) are one of the most common cancers worldwide. Colorectal carcinogenesis usually originates from colorectal adenomas that develop from normal mucosa and the adenocarcinoma sequence [6]. This process gives us a chance to early diagnose and intervene before the development of cancer. Colorectal adenomas are considered the most important precancerous lesions for CRC. These two diseases, colorectal adenomas and CRC, are collectively referred to as colorectal neoplasia.

Clarifying the pathogenesis and the risk factors of colorectal cancers is of great importance in the early diagnosis and treatment of this type of cancer [7]. Various previous studies have been conducted on this matter after H. pylori infection was accepted as a risk factor for colorectal cancer in the 1990s [8]. While some studies have determined a positive association between H. pylori infection and colorectal cancers [9–15], there are studies stating that this was controversial as well [16–19]. In addition, studies investigating the association between gastric IM and colorectal adenomas were also conducted [12, 20]. A recent study reported that there is a significant relationship between gastric intestinal metaplasia and colorectal neoplasia [21]. The aim of this study was to evaluate the relationship between H. pylori infection and IM, which is considered a premalignant lesion for gastric cancer, with colon neoplasia.
Subjects and methods

Ethics statement

Informed consent forms were obtained from the patients prior to the procedure. This study was approved by the Clinical Research Ethics Committee at Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital.

Subjects

A total of 214 patients, who were indicated for combined gastroscopy and colonoscopy with various prediagnoses between August 2016 and April 2020, were included in this retrospective study. Gastroscopic, histopathologic and demographic data of the patients were analyzed and recorded. Patients were separated into two groups according to their endoscopic biopsy results as IM positive and IM negative. Additionally, two groups were created according to the presence of H. pylori infection. The association between gastric intestinal metaplasia and H. pylori infection was evaluated. Patients with colon and gastric surgery histories, patients who had been administered eradication therapy for H. pylori, patients who had undergone previous polypectomies, patients with inflammatory bowel disease and patients with missing data were excluded from the study. The patients were fully sedated under the supervision of an anesthesiologist and were applied upper and lower endoscopy procedures by a single experienced endoscopist after a minimum of 8 h of fasting. The absence of abnormal appearance in the examinations was accepted as normal gastroscopic and colonoscopic examination, and biopsies were not taken. Biopsies were taken from patients whose endoscopic examination was suggestive of IM and from suspicious and abnormal lesions. Gastroscopy and colonoscopy procedures were performed with EG-600WR gastroscope and EC-600WL colonoscope (Fujinon, Tokyo, Japan), respectively.

Statistical analysis

All statistical analyses were performed with the Statistical Package (SPSS) 21.0 software. To evaluate the significance of the difference between the two groups, categorical variables were compared with the Pearson chi-square test or Fisher’s exact test, and continuous variables were compared using Student’s t-test. Two tailed \( p < 0.05 \) value was accepted as statistically significant.

Results

The patients included in the study were between the ages of 19 and 92, the mean age was 49.07 ± 15.80 and the median was 47. Furthermore, 89 (41.6%) of the patients were female and 125 (58.4%) were male. The number of IM positive and IM negative patients were 68 (31.8%) and 146 (68.2%) respectively. A total of 99 (46.3%) patients were positive for H. pylori, and 115 (53.7%) were negative. The patients were separated into two groups according to their H. pylori infection status (Table 1). There was no significant difference between the H. pylori positive and H. pylori negative groups in terms of mean age and gender. No correlation was found between H. pylori infection and colorectal neoplasm prevalence (\( p = 0.310 \)). Patients in the IM positive group were significantly older than the patients in the IM negative group (\( p = 0.000 \)), and there were a higher number of male patients in the IM positive group. Colorectal neoplasm prevalence was significantly higher in the IM positive group in comparison with the IM negative group (\( p = 0.033 \)). The distribution of patients according to IM status is presented in Table 2. All of the patients were separated into four groups (Table 3): Group A: IM positive, H. pylori negative; Group B: IM positive, H. pylori negative; Group C: IM negative, H. pylori positive; and Group D: IM negative, H. pylori negative. There was not any significant difference between these four groups in terms of colon neoplasm prevalence.

Discussion

Colon cancer is one of the leading causes of cancer related mortality and morbidities worldwide. Studies have been conducted regarding its etiology exploring the place of a high-fat animal-based diet, consumption of low-fiber foods, smoking [22]. There have been recent studies focusing on the probability of infectious agents, especially H. pylori, being associated as well. H. pylori infection is considered as the most important

| Table 1. Distribution of demographical characteristics of the patients according to the presence of Helicobacter pylori infection and their association with colon neoplasia. |
|---------------------------------|-----------------|-----------------|-----------------|
| Hp positive \( (n: 99) \)          | Hp negative \( (n: 115) \) | \( P \) value |
| Age, mean ± SD [years]           | 47.60 ± 15.44     | 50.34 ± 16.05     | 0.206           |
| Gender, \( n \) (%)              |                |                 | 0.546           |
| Male                             | 60(60.6)         | 65(56.5)         |                 |
| Female                           | 39(39.4)         | 50(43.5)         |                 |
| Colon pathology, \( n \) (%)     |                |                 |                 |
| Normal colon                     | 66(66.7)         | 84(73)           |                 |
| Colon neoplasm                   | 33(33.3)         | 31(27)           | 0.310           |

Hp; Helicobacter pylori.
The latest research has focused on the role of infectious agents in the prevention of colorectal cancers and the polyp–cancer spectrum [26, 27]. Although it is not fully understood how Helicobacter pylori infection increases the risk of colorectal neoplasia, according to the most commonly described pathogenesis, IM occurs after a long term Helicobacter pylori infection, and IM replaces normal gastric cells both in the corpus and the antrum [28]. The reduced gastric acid secretion triggered by IM causes hypergastrinemia, which may facilitate proliferation of colorectal mucosa, making the colon and rectum more susceptible to carcinogenesis [29, 30].

The association between Helicobacter pylori infection and colorectal neoplasia was first reported in 1997 [8]. Several previous studies showed that there was a positive correlation between Helicobacter pylori infection and colorectal neoplasia [10, 31–34]. In addition, this correlation was supported in other studies [35–37], and in a recent study, it was reported that Helicobacter pylori infection is an independent risk factor for colorectal adenomas [38]. In their 11-study meta-analysis, Zumkeller et al. [39] stated that Helicobacter pylori infection caused a minor increase in colorectal cancer risk. In our study, it was seen that there was no significant association between Helicobacter pylori infection and gender and age. Contrary to other reports that there was a correlation between Helicobacter pylori and colorectal neoplasia, in our study, a correlation was not found between Helicobacter pylori infection and colon neoplasm risk ($p = 0.310$). This outcome supports the studies reporting that Helicobacter pylori is not likely to increase the colorectal neoplasia risk.

AG and IM prevalence was found to be significantly higher in males in comparison with females [40]. There were many studies reporting that 50 years of age and above was an independent risk factor, and IM incidence increased in proportion to age [41, 42]. Similar to these studies, in our study, IM incidence was found as 41% in the group aged under 50, and 59% in the group aged 50 and over. Besides, IM incidence was higher in male patients in comparison with female patients.

In a comprehensive case-control study conducted on 156000 registered patients, a positive correlation was presented between IM and colorectal adenomas [12]. In their 2016 study conducted on 1641 patients aged 40 and over in China, Yan et al. analyzed gastric and colorectal biopsy results and found that Helicobacter pylori infection was significantly associated with a higher risk of colorectal adenoma [43]. In addition, an increase in the colorectal adenoma risk was seen in IM positive cases. Moreover, in another study, individuals with IM had a higher risk of having high-grade intraepithelial neoplasia [44]. There are very few studies evaluating the association between Helicobacter pylori and IM in Turkey. In our study, it was found that the IM positive group of patients had a significantly higher risk of colorectal neoplasia in comparison with the IM negative group of patients. There was not any significant difference in terms of colon neoplasia incidence in the analysis of four subgroups including both IM and HP. This result of the group analysis conducted according to the presence of IM supports other publications stating that IM brings a higher risk of colorectal adenoma. Having a limited number of patients in the groups might be the reason why the subgroup analysis gave this result.

Conclusions

Even though our study supports the idea that Helicobacter pylori infection increases the risk of colorectal neoplasia, this still remains a controversial issue. However, IM, which is considered a chronic sequela of Helicobacter pylori and a precursor lesion for gastric adenocarcinoma, was found to be a risk factor for colorectal neoplasia, similar to findings of many previous studies. In our study,
although *H. pylori* infection was not found to be a risk factor for colorectal neoplasia, it can be accepted as a potential risk factor for colorectal neoplasia development with IM. Therefore, patients with *H. pylori* infection and IM could be encouraged for colonoscopic examination in early stages of life to lower the colorectal neoplasia risk. However, it is obvious that there is a need for large-scale studies on this matter.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Data availability statement**

Endoscopic, histopathological, clinical and demographic data used to support the findings of this study are available from the corresponding author upon reasonable request.

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