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Is there any association between colonic polyps and gastric intestinal metaplasia?

STOMACH

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Original Article

ABSTRACT

Background/Aims: Chronic gastritis progression is a multistep process of atrophy, intestinal metaplasia (IM), and dysplasia, which may lead to invasive carcinoma. In this study, we identified an association of colonic polyps with gastric IM in patients undergoing colonoscopy.

Materials and Methods: This retrospective case-control, cross-sectional study was conducted in a tertiary-care institution in Turkey. Pathology and endoscopy reports were reviewed. The study group comprised 400 patients with colonic adenomatous polyps, and the control group comprised 360 patients without colonic adenomatous polyps on colonoscopy.

Results: The risk of gastric IM was 1.42-fold higher in the study group ($p<0.05$). The risk of IM in patients aged ≥50 years with colonic polyps was 3.35-fold higher than in those aged <50 years ($p<0.05$). The risk of *Helicobacter pylori* infection in the study group was 1.07-folder higher than that in the control group ($p<0.05$). *H. pylori* infection prevalence was higher only in patients with high-grade colonic polyp dysplasia ($p<0.05$). There were no statistically significant differences in the proportion of incomplete IM between the groups ($p<0.05$).

Conclusion: This study observed increased rates of gastric IM with colonic polyps. An increased risk of gastric IM was associated with higher grades of polyp dysplasia.

Keywords: *Helicobacter pylori*, intestinal metaplasia, colonic polyps, dysplasia

INTRODUCTION

Although its incidence varies, gastric cancer is the fourth-most prevalent cancer and the second-most common cause of cancer-related deaths worldwide (1). Intestinal-type gastric cancer, the most common subtype, is thought to develop by the carcinogenesis cascade defined by Correa (2). In this model, the progression of chronic gastritis is a multistep process of atrophy, intestinal metaplasia (IM), and dysplasia, which may lead to invasive carcinoma (2). Despite aggressive and expensive treatments, most patients with gastric adenocarcinoma die during the first year due to delayed diagnosis. Therefore, the early treatment and follow-up of patients with precancerous lesions, including IM and chronic atrophic gastritis, is important (3).

Although guidelines exist for some conditions, such as Barrett's esophagus, ulcerative colitis, and colonic polyps, there are no clear recommendations for gastric IM, a precancerous gastric lesion. The 2006 American Society for Gastrointestinal Endoscopy guidelines reported that most patients in the United States had a low risk of cancer progression; therefore, endoscopic surveillance for IM was not indicated for average-risk patients (4). According to the 2012 European Society of Gastrointestinal Endoscopy guidelines, patients with extensive atrophy and metaplasia should be followed up every 3 years (5). However, there are disagreements over the recommended follow-up of IM limited to the antrum and 3-year follow-up interval for extensive metaplasia (6).

Helicobacter pylori infection is a major risk factor for the development of gastric IM. A number of studies have reported an association of *H. pylori* infection with pathogenesis of colonic polyps and colorectal cancer (CRC). This infection is thought to increase the frequen-

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cy of colonic polyps and CRC. The effect of *H. pylori* infection on colonic polyps and CRC has been investigated in patients undergoing gastroscopy. In this study, we identified an association of colonic polyps with gastric IM in patients undergoing colonoscopy and determined if the location or number of colonic polyps or the presence of polyp dysplasia can be used to gastric atrophy or gastric IM.

MATERIALS AND METHODS

Data collection

This retrospective case-control, cross-sectional study was conducted at Başkent University Medical and Research Center, a tertiary-care institution in Konya, Turkey. Patient pathology and endoscopy reports from January 1, 2010 to December 31, 2013 were reviewed from the electronic database. We analyzed data of 1,475 patients over 18 years of age who underwent gastroscopy and colonoscopy on the same day at the gastroenterology clinic. Indications for gastrointestinal endoscopy included chronic diarrhea (10%), CRC screening (12%), weight loss (18%), anemia (22%), melena (4%), abdominal pain (21%), abdominal bloating (10%), and a positive fecal occult blood test (3%). Four gastroenterologists who had received the same gastroenterology fellowship training performed all endoscopies (Evis Exera II system, CLV-180, Olympus, Inc.; Tokyo, Japan).

We excluded 220 patients with inflammatory bowel disease, 237 without antrum or incisura biopsies, 98 with gastric cancer or CRC, 102 with inadequate bowel preparation, 38 with unsuccessful cecal intubation, and 20 with hyperplastic polyps.

Of the remaining 760 patients, demographic data and the presence of *H. pylori* infection, gastric atrophy, or IM were evaluated in antrum and incisura biopsy specimens. The study group comprised 400 patients with colonic adenomatous polyps, and the control group comprised 360 patients without polyps on colonoscopy. Patient selection is depicted in Figure 1.

Antrum and incisura biopsies were stained using hematoxylin–eosin and Giemsa stains. Metaplasia type was visualized using Periodic acid-Schiff (PAS) and Alcian Blue staining (PAS–Alcian blue stain). The number, location, and size of adenomatous polyps and the presence of dysplasia were also assessed in the study group. The location of colonic polyps was documented and classified as proximal colon, distal colon, or pan-colonic. The proximal colon included the transverse colon, hepatic flexure, ascending colon, and cecum. The distal colon included the rectum, sigmoid, descending colon, and splenic flexure. Polyps located in both were classified as pan-colonic. Advanced adenomas were defined as large adenomas (≥10 mm in size) or adenomas with histopathologic findings of villous or high-grade dysplasia.

The study was approved by the local Ethics Committee of Başkent University.

Statistical analysis

Data were analyzed using SPSS Statistics for Windows, Version 17.0. (SPSS Inc.; Chicago, IL, USA). The odds ratio (OR) was calculated to determine the association of two binary variables. Furthermore, logistic regression analysis was utilized to evaluate the relationships between risk factors of the binary variables; ORs were used to interpret these results. Differences between the means of two continuous variables were analyzed using t-tests, and differences between two proportions were analyzed using z-tests. Statistical analyses were performed using *R* (3.1.2). P values less than 0.05 were considered statistically significant in all analyses.

RESULTS

A total of 760 adult patients, 400 with colonic adenomatous polyps (study group) and 360 without polyps (control group), were included. Among the 400 patients with colonic polyps, 205 were men and 195 were women. The control group comprised 360 patients; 145 were men and 215 were women. OR was as 0.64 ($p<0.05$). Men had a 1.5-fold higher risk of colonic polyps than women (Table 1).

The mean overall age of the 760 patients was 57 years; the mean age for the study and control groups were 58 years (30–87 years) and 56 years (21–93 years), respectively. T-test analysis of these age differences was not statistically significant ($p>0.05$).

Demographic data and the presence of *H. pylori* infection, gastric atrophy, or IM were first analyzed for all 760 patients. Patients were classified as younger than 50 years or 50 years and older. Associations of risk factors (demographic data and presence of colonic polyps) with gastric IM, gastric atrophy, and *H. pylori* infection were analyzed by multiple logistic regression analyses (Table 2 and 3).

Table 1. Gender characteristics

	Gender		
	Male	**Female**	**Total**
Patients with colonic polyps (study group)	205	195	400
Patients without colonic polyps (control group)	145	215	360
Total	350	410	760

Table 2. Multiple logistic regression analysis for risk factors associated with gastric IM or atrophy

	Metaplasia		Atrophy	
Risk factor	**Odds ratio**	**p**	**Odds ratio**	**p**
≥50 years of age	2.76	<0.05	2.95	<0.05
Male gender	1.45	<0.05	1.50	<0.05
Presence of colonic polyps	1.42	<0.05	1.24	>0.05

IM: intestinal metaplasia

As shown in Table 2, the risk of developing gastric IM in patients aged ≥50 years was 2.76-fold higher than those aged <50 years (OR=2.76, p<0.05). The risk of developing gastric IM in men was 1.45-fold higher than in women (OR=1.45, p<0.05). In addition, the risk of gastric IM in the study group was 1.42-fold higher than that in the control group (OR=1.42, p<0.05).

The risk of gastric atrophy in patients aged ≥50 years was 2.95-fold higher than those aged <50 years (OR=2.95, p<0.05) (Table 2). Similarly, the risk of developing gastric atrophy was 1.5-fold higher in men than in women (OR=1.50, p<0.05). However, the risk of developing gastric atrophy did not significantly differ between the control and study groups (OR=1.24, p>0.05).

Unlike gastric IM and atrophy, the rate of *H. pylori* infection in patients aged <50 years was 1.15-fold higher than in those aged ≥50 years (Table 3). However, this difference was not statistically significant (OR=1.15, p>0.05). *H. pylori* infection was 1.30-fold more common among men than among women; this risk difference was also not statistically significant (OR=1.30, p>0.05). The risk of the presence of *H. pylori* infection in the study group was 1.07-fold higher than that in the control group (OR=1.33, p<0.05).

Risk factors that might be associated with IM and *H. pylori* infection in the study group were also examined. The results showed that the risk of developing gastric IM in patients with

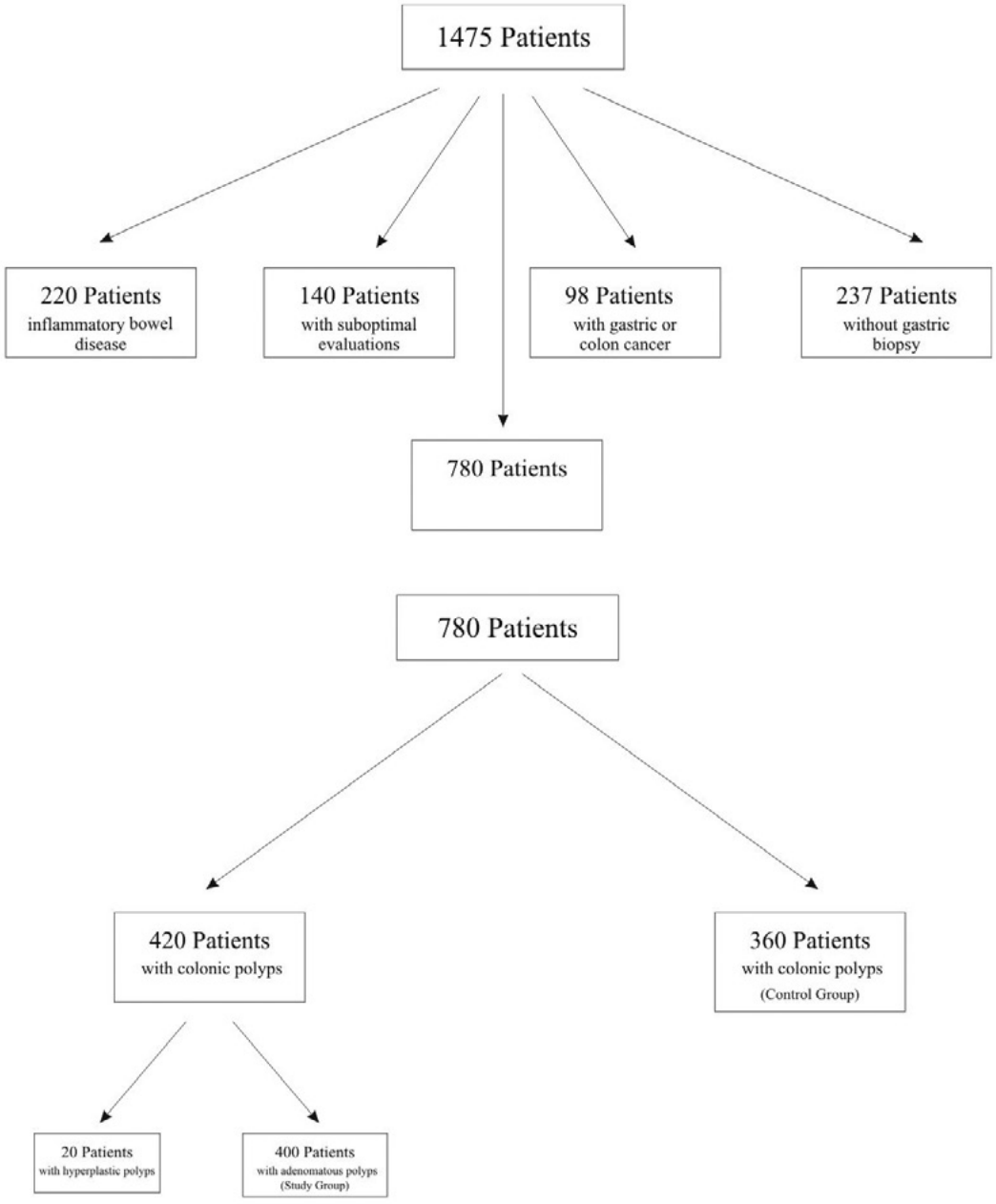

Figure 1. The scheme depicting patient selection

colonic polyps aged ≥50 years was 3.35-fold higher than in those aged <50 years (OR=3.35, p<0.05) (Table 4). Although the risk of developing IM was 1.47-fold higher in men with colonic polyps than women, the difference was not statistically significant (OR=1.47, p>0.05). The location or number of colonic polyps did not play a significant role in the risk of gastric IM in the study group (OR=1.04, p>0.05 and OR=1.13, p>0.05, respectively). The presence of advanced adenoma was associated with a significantly increased risk of gastric IM (OR=1.27, p<0.05).

The presence of *H. pylori* infection was higher only in patients with high-grade colonic polyp dysplasia (OR=1.32, p<0.05) (Table 5). Patient age or gender and the location and number of colonic polyps were not significantly associated with gastric dysplasia grade (OR=1.00, p>0.05; OR=1.30, p>0.05; OR=1.16, p>0.05; OR=1.05, p>0.05; OR=1.06, p>0.05, respectively).

Table 6 shows the number of the patients in both groups with incomplete and complete IM. According to the z-test for proportions of two samples, there was no statistically significant difference between the proportions of incomplete IM in these groups (p>0.05).

DISCUSSION

IM is the conversion of the superficial epithelium of oxyntic and antral mucosa into the intestinal epithelium. *H. pylori* infection is the main factor for the development of gastric IM. *H. pylori* infection can result in the development of chronic gastritis, glandular atrophy, IM, and dysplasia before carcinoma develops. Colonic polyps may be precursors of CRC through an adenoma-carcinoma sequence. The present study from a tertiary hospital investigated the association of IM with colonic polyps that may be precursors of malignancies in the gastrointestinal tract, and also determined if there were signs that might recommend gastroscopy in patients with polyps detected during colonoscopy. Our data showed that the risk of having gastric IM in patients with colonic polyps was than that in patients without colonic polyps (OR=1.42, p<0.05).

The risk of histopathologically determined *H. pylori* infection in the study group was higher than in the control group in this study, which is consistent with other reports (OR=1.33, p<0.05) (7-10). There was no statistical difference between the mean ages of the study and control groups in this study, but statistically more men had colonic polyps. This data showed that male patients had 1.5 times the risk of colonic polyps compared to female patients (OR=0.64, p<0.05). The increased rate of colonic polyps in men was also consistent with the literature (11,12). The analysis indicated that the risk of developing gastric IM in patients ≥50 years of age was 2.76 times higher than in patients <50 years (OR=2.76, p<0.05). The risk of developing gastric IM was 1.45 times higher in men than in women. This finding was also consistent with other reports (13).

Table 3. Multiple logistic regression analysis for risk factors associated with *H. pylori* infection

Risk factor	Odds ratio	p
<50 years of age	1.15	>0.05
Male gender	1.30	>0.05
Presence of colonic polyps	1.33	<0.05

Table 4. Multiple logistic regression analysis for risk factors associated with gastric intestinal metaplasia

Risk factor	Odds ratio	p
≥50 years of age	3.35	<0.05
Male gender	1.47	>0.05
Location of colonic polyps	1.04	>0.05
Number of colonic polyps	1.13	>0.05
Presence of advanced adenoma	1.27	<0.05

Table 5. Multiple logistic regression analysis for *H. pylori* infection-associated risk factors in the study group

Risk factor	Odds ratio	p
≥50 years of age	1.00	>0.05
Male gender	1.30	>0.05
Location of colonic polyps	1.16	>0.05
Number of colonic polyps	1.05	>0.05
Presence of advanced adenoma	1.32	<0.05
Grade of gastric dysplasia	1.06	>0.05

Table 6. Number of patients according to intestinal metaplasia type

	IM type		
	Incomplete	Complete	Total
Patients with colonic polyps	45	60	105
Patients without colonic polyps	25	47	72
Total	70	107	177

IM: intestinal metaplasia

Among common factors, *H. pylori* infection is most often associated with the pathogenesis of gastric IM and colonic polyps. The association of colonic polyps and CRC with *H. pylori* infection has been reported in many meta-analyses from 2006 to 2013. These previous studies have suggested that *H. pylori* infection leads to a 1.4–1.6-fold increased risk of colonic adenoma or CRC. *H. pylori* infection in patients with CRC or colonic polyps detected by serology and ^{13}C-urea breath tests (7-10). Recent publications have used immune-histochemical methods to detect *H. pylori* in colonic polyps and CRC tissues (14).

H. pylori-induced gastritis, atrophy, metaplasia, and cancer cascade in the gastric mucosa is now well accepted. Atrophy and hyper-gastrinemia developing during this cascade can have a

trophic effect on colonic mucosa. They can also contribute to the development of carcinogenicity, with a direct effect on the colonic mucosa. Most hypotheses about the effects of *H. pylori* infection effect on colonic polyps and CRC etiology are based on hypergastrinemia. Gastrin is the main hormone responsible for stimulation of gastric acid secretion. Additionally, gastrin and its derivatives exert proliferative and anti-apoptotic effects on the early stages of several types of cell tumors. This peptide structure hormone is synthesized as pre-pro-gastrin in the antral G cells. It is first converted to pro-gastrin by peptidase, and then converted to its biologically active amidated forms. Related to CRC, it is believed that gastrin has endocrine and paracrine effects on colorectal cells and also has trophic and anti-apoptotic properties. Research in recent years has indicated that pro-gastrin, previously thought to be an inactive form, is responsible for the carcinogenic effects. Furthermore, gastrin synthesized from tumor tissue also may have an autocrine effect. Increased gastrin levels are correlated with anti-apoptotic bcl-2 activity and increased tumorigenic and mutagenic cyclooxygenase-2 levels (15-18).

The second hypothesis regarding the effect of chronic *H. pylori* gastritis on colonic mucosa is that the infection results in enteric infections and bacterial overgrowth due to decreased gastric acid secretion. The impairment of gastric protein digestion due to hypochlorhydria and the fermentation of unabsorbed nutrients reaching the colon with excessive bacterial load may contribute to the development of CRC (19). In addition, the presence of *H. pylori* infection may be an indication of exposure to poor sanitation standards and frequent intestinal infections during childhood (20).

There is no consensus about the localization of colonic polyps and CRC in the presence of *H. pylori* infections. Although some literature reports suggest that colorectal adenomas are frequently observed in the left colon, other reports indicate that they are more often located in the proximal colon (21-23). These studies report that localization differences could be explained by chromosomal abnormalities during the development of left and right CRC (4). However, a study by Sonnenberg et al. (20) on 156000 patients did not report an association of the presence of *H. pylori* infection with the localization of colonic polyps or CRC. Similarly, our study did not find an association of *H. pylori* infection with the location of colonic polyps and gastric IM. The number of polyps did not play a statistically significant role in the risk of developing gastric IM in the study group (OR=1.04, p>0.05 and OR=1.13, p>0.05, respectively). However, increasing polyp dysplasia grades were significantly associated with an increased risk of gastric IM (OR=1.27, p<0.05).

After observing that colonic polyps were more frequent in patients with IM, we evaluated the association of gastric IM type with colonic polyps. Although there are reports that gastric cancer more frequently develops on a background of incomplete IM, several studies have also reported the opposite (24). In our study, the association of the presence of colonic polyps with IM type was evaluated in biopsies stained with PAS-Alcian blue, but a statistically significant difference was not observed in the prevalence of incomplete or complete IM in the study and control groups.

Several publications have reported that atrophic gastritis is not associated with increased CRC risk (25,26). Our study also found no statistically significant association in the risks of developing gastric atrophy in either the study or the control group (OR=1.24, p>0.05). Previous studies have not reported significant associations of colonic polyps with gastric atrophy. To our knowledge, there are no other reports on the association of colonic polyps with gastric IM. We believe that this positive association is related to the long-term course of IM. These data show that the frequent coexistence of colonic polyps and gastric IM may not be explained only by *H. pylori* infection and hypergastrinemic atrophic gastritis. A study by Fujimori et al. (27) in Japan reported a steadily decreasing prevalence of *H. pylori* infection, while the prevalence of CRC increased. Other factors besides *H. pylori* infection might increase the rate of CRC; however, further investigations are required.

This study had several limitations. Due its retrospective nature, all factors associated with gastrointestinal malignancies could not be further explored. The evaluation of smoking or nutritional habits, body mass index, family history of gastrointestinal malignancy, socioeconomic status, and use of aspirin and Non-Steroidal Anti Inflammatory Drugs (NSAIDs) might offer a better understanding of the etiopathogenesis of gastrointestinal malignancies. Additionally, previous antibiotic and proton pump inhibitor use should be evaluated. Insufficient corpus biopsy specimens prevented the classification of atrophy and metaplasia. We used routine biopsies, including antrum and incisura samples. Further studies including multiple gastric biopsies are necessary.

In conclusion, this study showed that the rate of gastric IM increases in the presence of colonic polyps. The risk of gastric IM increased with higher grades of polyp dysplasia. No association of gastric IM type with colonic polyps. Prospective multicenter studies may better explain the etiopathogenesis and association of the presence of gastric IM with colonic polyps.

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