Prevalence and predictors of colonoscopic findings in patients with autoimmune gastritis

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ABSTRACT

The clinical spectrum of autoimmune gastritis is silent in the early stages of the disease and no specific symptom is related to this entity. Although gastroscopic findings of this entity are well defined, data regarding colonoscopic findings are limited. The aims of this study were to determine the prevalence of colonoscopic findings and to explore factors that might affect these findings. This is a retrospective chart review of patients with autoimmune gastritis (n=240). Data regarding colonoscopic findings, serum gastrin and chromogranin A (CgA) levels and gastric histopathological results were extracted and compared with 550 patients positive for *Helicobacter pylori* and gastric atrophy. Control subjects had colonoscopy and gastroscopy with biopsies. Colorectal lesions were observed in 64 (26.6%) of patients with autoimmune gastritis and 36 (6.6%) patients had colorectal lesions in the control group (p<0.001). Serum gastrin (OR: 8.59, 95% CI 1.72 to 25.07, p<0.001) and CgA levels (OR: 6.79, 95% CI 0.41 to 27.26, p<0.001) were found as factors affecting the presence of colorectal carcinoma. Serum gastrin and CgA levels were also found as predictors for the presence of colorectal adenomas. There is a higher prevalence of colorectal neoplastic lesions in patients with autoimmune gastritis. Serum gastrin and CgA levels were found to be determinants of colorectal neoplastic lesions observed in patients. In the workup of these patients, serum gastrin and CgA levels may guide physicians for the demonstration of colorectal neoplastic lesions.

Significance of this study

What is already known about this subject?

- Autoimmune gastritis is an organ-specific autoimmune inflammatory disease of the stomach characterized by autoantibodies directed against some structures containing H+/K+-ATPase and intrinsic factor.
- In patients with autoimmune gastritis, hypergastrinemia occurs due to the damage to the oxyntic mucosa and achlorhydria, and gastrin stimulates the growth of epithelial cells and prevents apoptosis.
- Although upper gastrointestinal findings are well known, there are limited data regarding the colonoscopic findings in patients with autoimmune gastritis.

What are the new findings?

- There is a higher prevalence of colorectal neoplastic lesions in patients with autoimmune gastritis.
- Serum gastrin and chromogranin A levels were found to be determinants of colorectal neoplastic lesions observed in patients.

How might these results change the focus of research or clinical practice?

- Serum gastrin and chromogranin A levels and presence of intestinal metaplasia are useful parameters for the demonstration of colorectal neoplastic lesions.

INTRODUCTION

Autoimmune gastritis (AIG) is an organ-specific autoimmune inflammatory disease of the stomach characterized by autoantibodies directed against some structures containing H+/K+-ATPase and intrinsic factor. Immune destruction of the oxyntic glands leads to loss of gastric parietal cells, atrophy of the body, and hypochlorhydria/achlorhydria and hypergastrinemia.[1] These changes may result in deficiency of iron, vitamin B_{12} and potentially other micronutrients. AIG is usually asymptomatic in the early stages of the disease, and there are no specific symptoms related to this disease, therefore this may cause a delay in the diagnosis.[2] Symptoms of this disorder are variable, and most of the patients complain about dyspeptic symptoms, vitamin B_{12} and/or iron deficiency.[3] However, some patients may present with lower gastrointestinal (GI) symptoms such as diarrhea and/or vague abdominal pain. Although upper GI findings are well known, there is a paucity about the colonoscopic findings in patients with AIG.[3 4] In patients with AIG, hypergastrinemia occurs due to the damage to the oxyntic mucosa and achlorhydria. It has been shown that gastrin stimulates the growth of epithelial cells and prevents apoptosis.[5–9] Moreover, the proliferative effect of exogenous hypergastrinemia on in vitro colon cancer cell lines and in tumors in vivo has already been investigated extensively.[10–16]

The effect of gastrin in the pathogenesis of colorectal cancer development is mediated by several receptor subtypes. It has been shown that activation of these receptors takes place early in the adenoma-carcinoma sequence and gastrin may boost advancement through the adenoma-carcinoma sequence.[17] The hypothesis in this study was that, colorectal neoplastic lesions would be more common in patients with AIG due to endogenous hypergastrinemia. Therefore, the goals of this study were to investigate colonoscopic findings and to determine the possible factors that might affect these findings.

METHODS

Subjects

Medical records of patients diagnosed as having AIG (n=432) were analyzed retrospectively. However, colonoscopic examination results were available in 240 patients with AIG, thus the final analysis was performed in 240 patients. Data were collected regarding patient demographics, and colonoscopic and histopathological findings. Also investigated parameters were gastric histopathological findings, serum gastrin and chromogranin A (CgA) levels and presence of anti-parietal cell antibodies. A diagnosis of AIG in the gastric body had been established according to the pathological features in biopsy specimens, which were obtained during gastroscopic examination. Patients with uncertain histopathological findings were excluded from the study. Histopathologically, AIG is marked by chronic infiltration of inflammatory cells, disappearance of oxyntic glands, and parietal and zymogenic cells predominantly influencing the fundus and corpus of the stomach.[18]

Colonoscopic findings

Colonoscopic examination was performed in 240 patients and findings were classified as follows: normal, colorectal carcinoma, polyps. Pathological reports were retrieved from local pathological reports and polyps were categorized as (1) advanced adenoma (any adenoma ≥1 cm, high-grade dysplasia, or with tubulovillous or villous histology); (2) non-advanced adenoma (adenomas <1 cm without advanced histology); or (3) no adenoma.[19] The reason for colonoscopic investigation in 151 patients with AIG was diarrhea and/or lower GI symptoms (abdominal pain and/or weight loss) and 89 patients were investigated due to iron deficiency.

Gastric histopathological findings

Gastric biopsy specimens were assessed for the presence of chronic inflammation, neutrophil activity, atrophy, *Helicobacter pylori*, and intestinal metaplasia according to the updated Sydney system.[20]

Laboratory parameters

Serum CgA was determined by using available kits (CGA-ELISA CT; CIS Bio International, Gif-sur-Yvette Cedex, France). Serum gastrin level was assessed by DRG human gastrin 17-enzyme immunoassay kit (DRG International, Mountainside, New Jersey, USA). The presence of anti-parietal cell antibodies was tested with an indirect immunofluorescence test according to the instructions of the supplier (Euroimmun, Lübeck, Germany). Serum vitamin B_{12} concentration was determined using a chemiluminescence flow system (Beckman Access Method; Beckman Coulter, Brea, California, USA). The diagnosis of vitamin B_{12} deficiency was based on serum vitamin B_{12} levels <200 pg/mL.[21 22]

Control group

Five-hundred and fifty consecutive patients who had both gastric histopathological and colonoscopic findings were used as a control group. They were all positive for *H. pylori* and had gastric corpus atrophy and none of these patients had AIG detected histopathologically. The reason for colonoscopic investigation in the control group was mostly iron deficiency and for screening purposes. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki (6th revision, 2008). All authors had access to the study data and reviewed and approved the final manuscript.

Statistics

Descriptive statistics were shown as mean±SD for variables with normal distribution, as median (min-max) for variables with non-normal distribution. In cases where the number of groups was more than 2, the significance of the difference in terms of averages was investigated with the analysis of variance test, and the significance of the difference in terms of median values with the Kruskal-Wallis test. When there were 2 groups, for variables showing statistical significance, appropriate post hoc tests were used. Receiver operating characteristic (ROC) curves were used to describe and compare the performance of diagnostic values of serum gastrin and CgA levels on predicting colorectal neoplastic lesions. In order to find independent risk factors which might affect the presence of colorectal neoplastic lesions multivariable logistic regression analysis was used. In multivariate regression analysis, parameters that might affect univariate test results were defined and these parameters were used as candidate parameters for multivariate analysis by testing the backward method and a result model was established. ORs, CIs, and negative and positive predictive values (NPV and PPV) for significant parameters were determined. A p value <0.05 was accepted as significant.

RESULTS

In this study, 240 patients (mean age: 56.6 years, 121 men) with AIG were enrolled. These patients had undergone colonoscopic examination due to iron deficiency (n=89) and diarrhea and/or abdominal pain and/or weight loss (n=151). Baseline demographic, colonoscopic, histopathological and laboratory characteristics of patients with AIG and control group (mean age: 56.5 years, 364 women) are presented in tables 1 and 2. Colorectal lesions were observed in 64 (26.6%) patients (colorectal cancer in 14 (5.8%), advanced adenoma in 18 (7.5%), non-advanced adenoma in 32 (13.3%)). In the control group, there were 36 (6.6%) patients with colorectal lesions (colorectal cancer in 12 (2.2%), advanced adenoma in 11 (2%), non-advanced adenoma in 13 (2.4%)). While 38 (59.3%) out of 64 patients with AIG with colonoscopic lesions had iron deficiency, 51 (29%) out of 176 patients with AIG without colonoscopic lesions had iron deficiency (p=0.25). As for control group, 36 patients had colonoscopic lesions and 22

Table 1 Baseline and demographic characteristics of patients with autoimmune gastritis with and without colorectal neoplastic lesions

	All patients with AIG (n=240)	Patients with AIG without colonoscopic findings (n=176, 73.3%)	Advanced adenomas (n=18, 7.5%)	Non-advanced adenomas (n=32, 13.3%)	Colorectal carcinoma (n=14, 5.8%)	P value
Age (years±SD)	56.61±11.19	56.51±11.58	56.68±11	55.19±10.8	57.2±10.98	0.59
Gender (F/M)(%)	119/121 (49.6/50.4)	90/86 (51.1/48.9)	10/8 (55.5/44.4)	15/17 (46.9/53.1)	4/10 (28.6/71.4)	0.34
Body mass index (kg/m^2)	26.89±4.07	27.14±3.72	25.72±3.56	25.21±2.9	26.51±3.49	0.13
Inflammation	138/102 (57.5/42.5%)	86/90 (48.9/51.1%)	18/0 (100/0%)	20/12 (62.5/37.5%)	14/0 (100/0%)	<0.001
Activity (+/–)	154/86 (64.2/35.8%)	96/80 (54.5/45.5%)	18/0 (100/0%)	26/6 (81.2/18.8%)	14/0 (100/0%)	<0.001
Intestinal metaplasia (+/–)	145/95 (60.4/39.6%)	83/93 (47.2/52.8%)	18/0 (100/0%)	30/2 (93.8/6.3%)	14/0 (100/0%)	<0.001
Lower gastrointestinal symptom/iron deficiency	151/89 (62.9/37.1%)	125/51 (71/39%)	4/14 (22.2/77.8%)	14/18 (43.8/56.3%)	8/6 (57.1/42.9%)	0.25
APCA (+/–)	196/44 (81.7/18.3%)	143/33 (81.2/18.8%)	15/3 (83.3/16.7%)	26/6 (81.3/18.7%)	12/2 (85.7/14.3%)	0.19
Vitamin B_{12} (pg/L) (median)	188 (105–850)	199 (165–850)	187 (170–430)	189 (172–530)	186 (105–390)	0.12
Chromogranin A (ng/mL) (min-max)	268.37±163.68	178.12±68.21	430.21±55.87	368.25±51.62	635.68±84.1	0.001
Gastrin (pg/mL) (min-max)	592.95±223.34	430.6±199.25	712.31±131.52	654.28±104.41	992.78±249.88	0.001

AIG, autoimmune gastritis; APCA, anti-parietal cell antibody.

of these patients were investigated due to iron deficiency. In the control group, the ratio of patients with colonoscopic lesions who had undergone colonoscopic examination due to iron deficiency (n=22, 61.1%) was higher compared with patients with AIG with colonoscopic lesions (n=38, 59.3%) (p<0.001). Overall, colorectal lesions were more common in patients with AIG compared with control group (p<0.001). Laboratory findings revealed that CgA levels were higher in patients with colorectal lesions compared with patients without colorectal lesions (178.12±68.21 ng/mL vs 430.21±55.87 in advanced adenomas, 368.25±51.62 ng/mL in non-advanced adenomas, 635.68±84.1 ng/mL in colorectal carcinoma, p<0.001). Serum gastrin levels were also higher in patients with colorectal lesions compared with patients without colorectal lesions (430.6±199.25 pg/mL vs 712.31±131.52 pg/mL in advanced adenomas, 654.28±104.41 pg/mL in non-advanced adenomas, 992.78±249.88 pg/mL in colorectal carcinoma, p<0.001). There were no differences between groups by means of serum vitamin B_{12} levels and presence of anti-parietal cell antibodies.

In our study, the CgA value of patients with AIG without colonoscopic findings was 178.12±68.21 ng/mL. Among the patients with AIG with colonoscopic findings, the CgA level was 368.25±51.62 ng/mL in the non-advanced adenoma group, 430.21±55.87 ng/mL in the advanced adenoma group, and 635.68±84.1 ng/mL in the colorectal carcinoma group, respectively. Serum gastrin level was 430.6±199.25 pg/mL among patients with AIG without colonoscopic findings. Among the patients with AIG with colonoscopic findings, gastrin value was 654.28±104.41 pg/mL in the non-advanced adenoma group, 712.31±131.52 pg/mL in the advanced adenoma group, and 992.78±249.88 pg/mL in the colorectal carcinoma group, respectively.

Table 2 Baseline and demographic characteristics of control subjects with and without colorectal neoplastic lesions

	Control group (n=550)	Without colonoscopic lesions (n=514, 93.5%)	Advanced adenomas (n=11, 2%)	Non-advanced adenomas (n=13, 20.4%)	Colorectal carcinoma (n=12, 2.2%)	P value
Age (years±SD)	56.58±10.59	56.17±9.8	56.98±10.1	61.26±9.87	66.28±10.19	0.25
Gender (F/M)(%)	364/186 (66.2/33.8)	347/167 (67.5/32.5)	3/8 (27.3/72.7)	4/9 (30.8/69.2)	6/6 (50/50)	<0.001
Body mass index (kg/m^2)	27.31±2.78	27.2±2.48	27.69±2.3	27.21±3.1	28.12±2.14	0.13
Inflammation (+/–)	538/12 (97.8/2.2%)	502/12 (97.7/2.3%)	11/0 (100/0%)	13/0 (100/0%)	12/0 (100/0%)	0.29
Activity (+/–)	544/6 (98.9/1.1%)	508/6 (98.8/1.2%)	11/0 (100/0%)	13/0 (100/0%)	12/0 (100/0%)	0.41
Intestinal metaplasia (+/–)	204/346 (37.1/62.9%)	170/344 (33/67%)	9/2 (81.8/18.2%)	13/0 (100/0%)	12/0 (100/0%)	<0.001
Lower gastrointestinal symptoms/iron deficiency	339/211 (61.6/38.4%)	326/188 (63.4/36.6%)	6/5 (54.5/45.5%)	8/5 (61.5/38.5%)	0/12 (0/100%)	<0.001

Table 3 Univariate and multivariate analyses of factors associated with colorectal carcinomas

	Univariate analysis			Multivariate analysis		
Colorectal carcinoma	OR	95% CI	P value	OR	95% CI	P value
Age	1.91	1.12 to 48.61	0.12			
Gender	0.48	1.51 to 27.93	0.012			
Inflammation (+)	1.47	0.98 to 20.45	<0.001	2.49	2.38 to 19.56	0.004
Activity (+)	1.11	0.63 to 7.12	0.044	2.24	1.03 to –9.35	0.03
Intestinal metaplasia (+)	3.11	0.82 to 7.3	0.001	4.74	1.28 to 20.9	0.001
APCA	0.71	0.6 to 1.35	0.072			
Vitamin B_{12} (pg/L) (median)	0.73	0.51 to 2.97	0.6			
Chromogranin A (µg/L) (min-max)	3.24	0.24 to 10.5	0.003	6.79	0.41 to 27.26	0.011
Gastrin (ng/L) (min-max)	5.15	3.02 to 14.28	0.017	8.59	1.72 to 25.07	0.001

APCA, anti-parietal cell antibody.

In the multivariate analysis, serum gastrin (OR: 8.59, 95% CI 1.72 to 25.07, p<0.001) and CgA levels (OR: 6.79, 95% CI 0.41 to 27.26, p<0.001) were found as factors affecting the presence of colorectal carcinoma. Serum gastrin and CgA levels were also found as predictors for the presence of colorectal adenomas (table 3). The cut-off values for serum gastrin (area under the ROC (AUROC) 84.8, 95% CI 79.9 to 89.7; sensitivity 84.6, 95% CI 75.0 to 90.9; specificity 85.0, 95% CI 77.8 to 90.2; PPV: 77.6 (71.2–83.4); NPV: 90.1 (84.8–93.6), p<0.001) and CgA levels (AUROC 93.1, 95% CI 89.7 to 96.6; sensitivity 88.4, 95% CI 79.5 to 93.8; specificity 96, 95% CI 91.1 to 98.3; PPV: 93.2 (88.6–96.1); NPV: 93.1 (88.5–96.1), p<0.001) were 694 pg/mL and 412 ng/mL, respectively, in predicting the existence of colorectal carcinoma/adenomas (figure 1A,B).

DISCUSSION

This study investigated the prevalence and factors affecting colonoscopic manifestations in patients with AIG. In this study, we observed a high prevalence of colorectal carcinoma and adenomas in patients with AIG compared with a group of patients positive for *H. pylori* and gastric atrophy. We selected patients positive for *H. pylori* and gastric atrophy in order to investigate the differences between AIG and *H. pylori*-induced atrophic gastritis regarding colonoscopic findings. Talley *et al*[23] identified 150 patients with pernicious anemia with a median follow-up of 10.9 years and found 15 colorectal adenocarcinoma cases. They suggested that patients with pernicious anemia may be at a small increased risk for the development of colon cancer especially in the 5 years of diagnosis.[3] In our study, the frequency of advanced and non-advanced adenomas was found to be higher in patients with AIG compared with the control group and the determinants of presence of colorectal carcinoma and adenomas were serum gastrin and CgA levels with a cut-off value of 694 pg/mL and 412 ng/mL, respectively. There are several potential explanations for a relation between AIG and colon carcinoma and adenomas. In these patients, serum gastrin levels were continuously high and sustained due to failure in the acid-gastrin feedback loop.[24] It has been shown that gastrin plays a role as a growth factor for colorectal cancer at physiological concentrations and premalignant adenomas were also shown to express an isoform of the cholecystokinin B/gastrin receptor.[25] Renga *et al* investigated the effect of gastrin on colorectal cell proliferation in patients with AIG and Zollinger-Ellison syndrome and in 16 control subjects by using rectal biopsy specimens in order to study rectal cell kinetics.[26] They found that the labeling frequency in the upper two-fifths of the glands was higher in patients with chronic atrophic gastritis or Zollinger-Ellison syndrome compared with control subjects. They concluded that

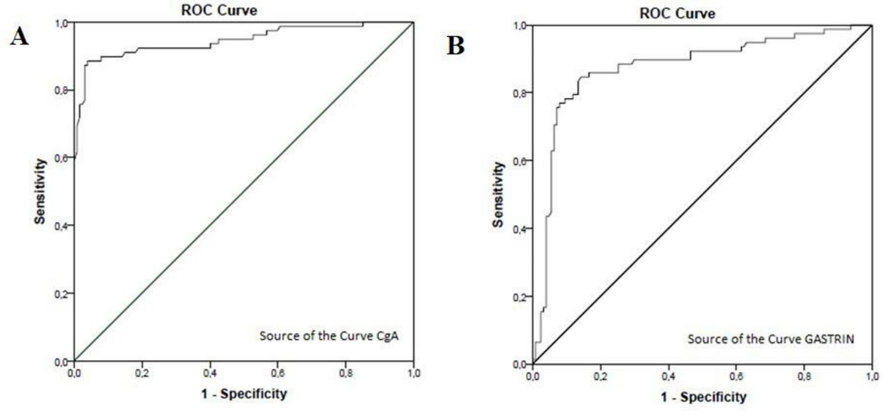

Figure 1 Receiver operating characteristic (ROC) curves for chromogranin A (CgA) (A) and gastrin (B) levels as predictors of colorectal neoplastic lesions.

endogenous hypergastrinemia is related with rectal cell proliferation defects, similar to those observed in conditions at high risk for colon cancer. Lahner *et al* investigated 160 patients with hypergastrinemia with atrophic gastritis and 160 healthy subjects by means of colonoscopic examination. They found neoplastic colorectal lesions in 28 patients with atrophic gastritis and in 36 control subjects (p=0.33) and reported that hypergastrinemia does not increase the risk of neoplastic colorectal lesions and a closer surveillance of colonic neoplasia in patients with hypergastrinemic atrophic gastritis is not necessary.[27] Boursi *et al* evaluated the relationship between pernicious anemia and colorectal cancer risk in a large population adjusted to common colorectal cancer risk factors including 154 cases with colorectal carcinoma and 563 control subjects.[28] In this study, they did not find an association between pernicious anemia and colorectal cancer risk.

It has been shown that *H. pylori* infection contributes to colorectal carcinogenesis via gastrin secretion by inducing higher mucosal cell proliferation in the colon.[29] In this context, Machida-Montani *et al* studied the relationship between *H. pylori*, serum gastrin level, and atrophic gastritis with colorectal carcinoma.[30] They included 113 cases with colorectal carcinoma and 226 control subjects and concluded that *H. pylori* and atrophic gastritis did not increase the risk of colorectal carcinoma; however, atrophic gastritis may increase the risk of rectal cancer. In another study, Lee *et al* investigated the association between *H. pylori* infection status, atrophic gastritis and advanced colorectal neoplasm (CRN) in a cross-sectional study in 6351 consecutive asymptomatic subjects who underwent a screening colonoscopy.[31] They found that 316 subjects (5.0%) had advanced CRN. *H. pylori* seropositivity was 61.3% and the presence of *H. pylori* infection was associated with advanced CRN (OR: 1.49, 95% CI 1.17 to 1.91, p=0.001). *H. pylori* infection was associated with an increased risk of advanced CRN (OR: 1.34, 95% CI 1.04 to 1.72, p=0.023). *H. pylori*-related atrophic gastritis was significantly associated with the risk of advanced CRN (OR: 1.40, 95% CI 1.03 to 1.91, p=0.030), whereas *H. pylori* infection without atrophic gastritis was not. Our patients with AIG were all negative for active *H. pylori* infection and the control group included patients positive for *H. pylori* with atrophic gastritis. In this study, another predictor of colorectal neoplastic lesions was CgA levels (OR: 6.74, 95% CI 0.41 to 27.26, p<0.001). It was reported that there was a positive correlation between serum gastrin and CgA levels in patients with AIG.[32] The possible explanation for this finding can be the effect of gastrin on gastric enterochromaffin-like cells because it is stated that enterochromaffin-like cell mass is a major determinant of CgA elevation in hypergastrinemic conditions.[33] In our study, gastric intestinal metaplasia was also found as a predictor of colorectal carcinoma (OR: 4.74, 95% CI 1.28 to 20.9, p<0.001). In a case–control study, Sonnenberg and Genta investigated 156.000 enrolled patients who underwent colonoscopy and esophagogastroduodenoscopy with biopsy results, and also showed a positive correlation between intestinal metaplasia and colorectal adenomas.[34]

Some limitations of the study must be mentioned. First, this was a retrospective study which might cause a selection bias. Second, several important risk factors for colorectal cancer such as smoking history, alcohol consumption, diabetes, chronic aspirin/non-steroidal anti-inflammatory drug use and hormone replacement therapy were not taken into account due to the retrospective nature of the study. Nonetheless, this is the largest cohort of patients with AIG that has been described so far, showing that colonoscopic lesions are frequent in these patients.

In conclusion, a higher prevalence of colorectal neoplastic lesions was observed in patients with AIG. Major factors that might affect the presence of colorectal neoplastic lesions were serum gastrin and CgA levels. In the workup of these patients, serum gastrin and CgA levels and presence of intestinal metaplasia should be useful for the demonstration of colorectal neoplastic lesions.

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