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【 ORIGINAL ARTICLE 】

Characteristics of Early Gastric Cancer in a Patient with a History of *Helicobacter pylori* Infection and No History of Eradication Therapy

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Abstract:

Objective The characteristics of gastric cancer in patients with atrophic mucosa and no apparent history of *Helicobacter pylori* eradication have not been thoroughly investigated. Therefore, this study examined the clinicopathological characteristics of gastric cancer in these patients.

Methods We retrospectively examined the endoscopic and pathological characteristics of gastric cancer in patients who underwent endoscopic submucosal dissection.

Patients We divided the patients into 2 groups: those with gastric atrophy and no history of eradication (group A; n=102) and those with a history of eradication (group B; n=161). In group A, patients were further divided into mild atrophy (group C) and severe atrophy (group D) groups, while group B was further divided into those who underwent eradication treatment >5 years ago (group E) and those who underwent eradication 1-5 years ago (group F).

Results Group A comprised significantly older individuals (75±8.0 vs. 71±7.5 years old, p<0.001) with a higher frequency of elevated gastric cancer than group B (32.4% vs. 17.4%, p=0.006). Compared with group E, group A was older and had a greater incidence of elevated gastric cancer. The incidence of gastric cancer in the U or M region was lower in group C than in group D.

Conclusion Gastric cancer in patients with gastric atrophy and no history of eradication was associated with an older age and higher frequency of elevated-type morphology than in those with a history of eradication.

Key words: autoimmune gastritis, eradication, gastric cancer, *Helicobacter pylori*

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Introduction

Helicobacter pylori infection is the most critical risk factor for gastric cancer (1-3). Therefore, its eradication is important for mitigating the occurrence of *de novo* gastric cancer and thwarting metachronous recurrence after endoscopic therapy (4-7). However, a persistent risk of gastric cancer development has recently been reported despite the protracted success of *H. pylori* eradication therapy (8). Therefore, understanding the clinical and endoscopic characteristics of gastric cancer that arises after eradication therapy for *H. pylori* has gained great interest (9-12).

Gastric cancer can occur in *H. pylori*-negative atrophic

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mucosa without an obvious history of eradication therapy. Such patients had previously been infected with *H. pylori*, which had disappeared even without undergoing eradication treatment. To our knowledge, however, no studies have compared the characteristics of gastric cancer that arises in *H. pylori*-negative atrophic gastric mucosa, both with and without eradication treatment.

This study evaluated the clinical, endoscopic, and pathological features of early gastric cancer resected via endoscopic submucosal dissection (ESD) in patients previously infected with *H. pylori* with no documented history of eradication therapy and compared them to the features of patients with a confirmed history of eradication therapy.

Materials and Methods

The evaluation of the H. pylori status

For most evaluated patients, *H. pylori* eradication was performed at institutions other than our hospital. Consequently, we conducted a thorough examination of medical records to ascertain whether or not eradication success was explicitly documented. In patients who did not undergo eradication, we confirmed that anti-*H. pylori* antibody titers were <10, as determined using the Eiken E-plate test. In all patients, the absence of *H. pylori* infection was confirmed by a histological analysis of the background gastric mucosa.

Endoscopic atrophy

Endoscopic gastric atrophy was evaluated according to the Kimura-Takemoto classification (13).

Histological analyses

Three biopsy specimens were obtained: one each from the greater curvature of the antrum, the lesser curvature of the corpus, and the greater curvature of the corpus. Gastric mucosa samples were evaluated in accordance with the updated Sydney system for the degree of inflammation (mononuclear cell infiltration), atrophy, and intestinal metaplasia (14). Two experienced pathologists from Okayama University Hospital performed histological evaluations.

Definition of previous infection with H. pylori with no history of eradication therapy (group A)

Group A (no eradication history group) was defined as patients with atrophic gastric mucosa without current infection or a history of eradication therapy for *H. pylori*. A patient was considered to be in group A if all of the following criteria were met: (1) no clear history of *H. pylori* eradication, (2) gastric atrophy was observed according to the Kimura-Takemoto classification (C-2 or higher), (3) biopsy specimens were pathologically *H. pylori* negative, and (4) seronegative for *H. pylori* antibody.

Autoimmune gastritis (AIG)

In this study, we analyzed patients with AIG, which typically manifests as corpus-predominant atrophy. Thus, we suspected AIG in patients who showed a significant presence of atrophic mucosa in the gastric corpus compared to the antrum via an endoscopic or histological evaluation. Furthermore, AIG should be considered a potential diagnosis in patients with pan-atrophic gastric mucosa, particularly in the absence of a clear history of eradication therapy. Consequently, when encountering patients with severe atrophy (O-2 or O-3) with no history of eradication therapy, we conducted an immunostaining analysis of biopsy specimens obtained from both the greater curvature of the antrum and corpus. Specifically, we used chromogranin A, a well-established screening marker for gastric enterochromaffin-like cell hyperplasia (15). In addition, gastric parietal cells and intrinsic factor antibodies were quantified in all cases where AIG was suspected based on the presence of corpus-predominant atrophy or immunostaining findings. AIG was diagnosed based on the presence of gastric parietal cells or intrinsic factor antibodies.

Patients

A total of 816 patients underwent ESD for the management of early gastric cancer at Okayama University Hospital between January 2013 and December 2020 after the exclusion of patients with a remnant stomach or gastric tube (Fig. 1). Individuals who were currently infected with *H. pylori* (n=165), those who had never been infected with *H. pylori* (n=20), and those lacking sufficient data pertaining to their *H. pylori* infection status (n=305) were excluded. Furthermore, patients presenting with adenocarcinoma of the fundic gland type (n=11) were excluded because this particular cancer variant is considered to occur independent of the *H. pylori* infection status (16). Four patients were diagnosed with AIG. Of the remaining 311 patients, 102 presented with no discernible history of eradication therapy (group A: no eradication history), whereas 209 had previously undergone eradication therapy. Furthermore, patients who developed gastric cancer within 1 year after the completion of eradication therapy and those whose specific timeframe of eradication remained unclear (n=48) were excluded because they might have harbored undetected cancer before the therapy was successful and consequently could have been influenced by the presence of *H. pylori* infection (17-19). Finally, group A, the cohort with no history of eradication therapy, included 102 patients, whereas group B, the eradication group, included 161 patients.

Patients presenting with *H. pylori*-negative, atrophic mucosa or no eradication history were divided into three distinct groups: 1) those who inadvertently underwent eradication through the administration of antibiotics for ailments unrelated to *H. pylori*; 2) those who had unintentionally forgotten their history of *H. pylori* eradication; and 3) those who experienced spontaneous elimination of *H. pylori* as a result of the advancement of severe gastric mucosal atrophy (20). Of these, the third group (comprising patients with spontaneous *H. pylori* clearance) was more prone to severe

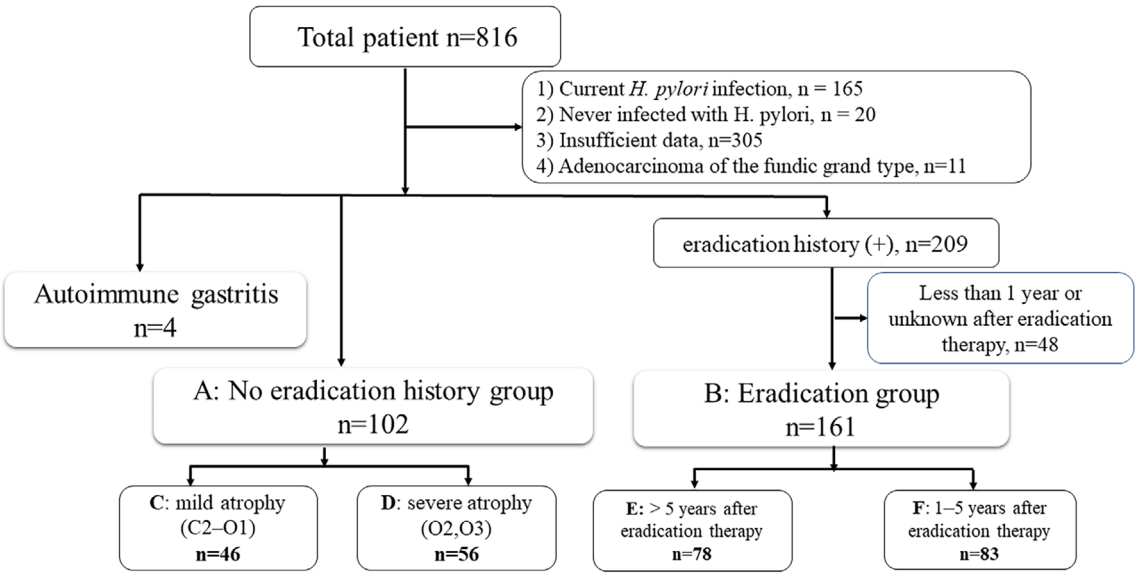

Figure 1. The flowchart of patient enrollment.

atrophy (O-2 or O-3) than the others, whereas the other two groups showed varying degrees of gastric atrophy. Therefore, we proceeded with subgroup categorization within group A, distinguishing between patients with mild atrophy (group C) and those with severe atrophy (group D), to conduct a more detailed analysis. Kamada et al. reported that improvement in gastritis with eradication might have contributed to the detection of gastric cancer within 48 months of eradication (9). Therefore, we further subdivided group B into two distinct subgroups: those who had surpassed a post-eradication period of over 5 years (group E) and those who had experienced a post-eradication duration of 1-5 years (group F).

Study design

This was a retrospective cohort study conducted at a single center. First, we comprehensively compared clinicopathological data between groups A and B. In the subsequent subgroup analysis, we compared the clinicopathological data and histological background of the gastric mucosa between groups A and E, which comprised individuals who underwent *H. pylori* eradication for over five years. Furthermore, we investigated the impact of the degree of atrophy on the clinicopathological characteristics by comparing group C (with mild atrophy) with group D (with severe atrophy), and finally, we compared clinicopathological data between groups B and D in order to exclude those who inadvertently underwent eradication through the administration of antibiotics, and those who had unintentionally forgotten their history of eradication.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Okayama University Graduate School of Medicine (Reference No.: 2203-029). Informed consent to be included in the study or equivalent was obtained from all patients.

Statistical analyses

All statistical analyses were performed using the chi-square test and logistic regression analysis using the JMP® Pro 15 software package (SAS Institute, Cary, USA), and p values <0.05 were considered statistically significant.

Results

Clinicopathological characteristics of patients with no eradication history of H. pylori

Table 1 shows the clinicopathological characteristics of patients with no history of *H. pylori* eradication (group A), who were significantly older than those with an eradication history (group B) (mean age±standard deviation: 75±8.0 vs. 71±7.5 years old, p<0.001). Group A had a higher incidence of elevated gastric cancer than group B (32.4% vs. 17.4%, p =0.006). Statistically significant differences in age and prevalence of elevated gastric cancer were observed between groups A and B using a multivariate analysis. Table 2 presents the clinicopathological characteristics of patients with no history of eradication (group A) compared to those of patients who had been receiving eradication treatment for *H. pylori* for a considerable duration (over 5 years) (group E). In addition to being older (mean age: 75±8.0 vs. 71±8.0 years old, p=0.001) and having a greater incidence of elevated-type gastric cancer (32.4% vs. 14.1%, p=0.004), a univariate analysis revealed a higher prevalence of open-type atrophy in group A than in group E (83.3% vs. 69.2%, p= 0.03). However, the statistical significance of open-type atrophy prevalence diminished in the multivariate analysis. During the analysis of the background gastric mucosa in both groups (Table 3), group A showed a significantly higher frequency of inflammation (52.0% vs. 35.9%, p=0.03), atrophy (36.3% vs. 16.7%, p=0.003) and intestinal metaplasia

Table 1. Clinicopathological Characteristics of the Patients with No Eradication History of *H. pylori*.

	A: previous infection with no eradication (n=102)	B: eradication therapy (n=161)	p value	Multiple logistic regression		
				OR	95% CI	p value
Age mean age±SD	76±8.2	71±7.4	<0.001	1.99*	1.18-3.37*	0.010*
Male gender, n (%)	76 (74.5)	123 (76.4)	0.73			
Open type atrophy, n (%)	85 (83.3)	122 (75.8)	0.14	1.52	0.78-2.97	0.22
Location of U+M, n (%)	60 (58.8)	111 (68.9)	0.09	0.68	0.39-1.19	0.18
Elevated type, n (%)	33 (32.4)	28 (17.4)	0.006	2.10	1.16-3.83	0.01
Well differentiated type, n (%)	88 (86.3)	145 (90.1)	0.35			
Sm, n (%)	17 (16.7)	24 (14.9)	0.70			

*Age ≥75

Table 2. Clinicopathological Characteristics of Patients with No History of Eradication (Group A) Compared with Those of Patients Who Underwent Eradication Treatment >5 Years Ago (Group E).

	A: previous infection with no eradication (n=102)	E: eradication treatment >5 years ago (n=78)	p value	Multiple logistic regression		
				OR	95% CI	p value
Age mean age±SD	75±8.0	71±8.0	0.001	2.11*	1.12-3.98*	0.02*
Male gender, n (%)	76 (74.5)	62 (79.5)	0.43			
Open type atrophy, n (%)	85 (83.3)	54 (69.2)	0.03	1.83	0.87-3.84	0.11
Location of U+M, n (%)	60 (58.8)	51 (65.4)	0.37			
Elevated type, n (%)	33 (32.4)	11 (14.1)	0.004	2.56	1.16-5.64	0.02
Well differentiated type, n (%)	88 (86.3)	69 (88.5)	0.66			
Sm, n (%)	17 (16.7)	6 (7.7)	0.07	2.67	0.96-7.45	0.06

*Age ≥75

Table 3. Comparison of the Background Gastric Mucosa.

	A: previous infection with no eradication (n=102)	E: eradication treatment >5 years ago (n=78)	p value
Antrum			
Inflammation+, n (%)	63 (61.8)	54 (69.2)	0.30
Atrophy+, n (%)	77 (75.5)	58 (74.4)	0.86
Intestinal metaplasia+, n (%)	65 (63.7)	43 (55.1)	0.24
Lesser curvature of the corpus			
Inflammation+, n (%)	76 (74.5)	57 (73.1)	0.83
Atrophy+, n (%)	83 (81.4)	57 (73.1)	0.19
Intestinal metaplasia+, n (%)	76 (74.5)	51 (65.4)	0.18
Greater curvature of the corpus			
Inflammation+, n (%)	53 (52.0)	28 (35.9)	0.03
Atrophy+, n (%)	37 (36.3)	13 (16.7)	0.003
Intestinal metaplasia+, n (%)	29 (28.4)	7 (9.0)	0.001

(28.4% vs. 9.0%, p=0.001) in the greater curvature of the corpus than group E.

A comparison of the clinicopathological characteristics between the severe atrophy group and mild atrophy groups

Group A was further divided into groups C (C-2 to O-1) and D (O-2 or O-3), according to the Kimura-Takemoto classification, and a comparative analysis of the clinicopathological characteristics of these groups was conducted (Table 4). The incidence of gastric cancer in the upper two-thirds (U or M region) was lower in group C than in group D (47.8% vs. 67.9%, p =0.04).

A comparison of the clinicopathological characteristics between patients with an eradication history (group B) and patients with severe atrophy and no eradication (group D)

Table 5 shows the clinicopathological characteristics of patients with severe atrophy and no history of *H. pylori* eradication (group D). Patients in group D were significantly older than those with an eradication history (group B) (mean age±standard deviation: 74±8.6 vs. 71±7.5 years, p=0.001). Group D had a higher incidence of elevated gastric cancer

Table 4. Comparison of Clinicopathological Characteristics between Severe Atrophy Group and Mild Atrophy Group.

	C: mild atrophy (n=46)	D: severe atrophy (n=56)	p value
Age mean age±SD	76±6.8	75±6.4	0.58
Male gender, n (%)	31 (67.4)	45 (80.4)	0.13
Location of U+M, n (%)	22 (47.8)	38 (67.9)	0.04
Elevated type, n (%)	11 (23.9)	22 (39.3)	0.10
Well differentiated type, n (%)	40 (87.0)	48 (85.7)	0.86
Sm, n (%)	5 (10.9)	12 (21.4)	0.15

Table 5. Comparison of Clinicopathological Characteristics between Patients with Eradication History (Group B) and Patients with Severe Atrophy and No Eradication (Group D).

	B: eradication history (n=161)	D: severe atrophy with no eradication (n=56)	p value
Age mean age±SD	71±7.4	74±8.6	0.001
Male gender, n (%)	123 (76.4)	45 (80.4)	0.54
Location of U+M, n (%)	111 (68.9)	38 (67.9)	0.88
Elevated type, n (%)	28 (17.4)	22 (39.3)	0.001
Well differentiated type, n (%)	145 (90.1)	48 (85.7)	0.38
Sm, n (%)	24 (14.9)	12 (21.4)	0.27

than group B (39.3% vs. 17.4%, p=0.001). Furthermore, we compared patients with severe atrophy (type O-2 or O-3) in groups B (group B (O-2, O-3) and D (Table 6). Group D showed a higher incidence of elevated gastric cancer than group B (O-2, O-3) (39.3% vs. 16.0%, p=0.002). These results were similar to those of other examinations (group A vs. group B, and group A vs. group E).

AIG in the spontaneous eradication group

No instances of corpus-dominant atrophy coexisting with antrum preservation were detected through endoscopic or histological analyses. An immunostaining analysis of patients with severe atrophy (O-2 or O-3) and no discernible history of eradication therapy (group D) revealed enterochromaffin-like cell hyperplasia and positive staining for chromogranin A in 4 patients (6.7%), all of whom tested positive for gastric parietal cell antibodies, whereas one patient tested positive for intrinsic factor antibodies. Consequently, these four patients were diagnosed with AIG, and the gastric cancer detected in these 4 patients was localized to the lower portion of the stomach, with 3 (75%) experiencing elevated gastric cancer and 1 experiencing deep submucosal invasion.

We further report a typical case of *H. pylori* infection in a patient with no history of eradication therapy (Fig. 2).

Discussion

In the present study, we examined the clinicopathological characteristics of gastric cancer in patients with and without a history of *H. pylori* eradication and uncovered several distinct attributes of gastric cancer in individuals with no identifiable eradication history. Compared to the positive eradication history group, patients with no eradication history were significantly older and exhibited a higher incidence of elevated gastric cancer. The older age of patients with no history of eradication can be reasonably attributed to the spontaneous elimination of *H. pylori* due to the prolonged progression of gastric mucosal atrophy to a point where *H. pylori* can no longer survive (20).

An analysis of the background gastric mucosa revealed a notable prevalence of atrophy and intestinal metaplasia in the greater curvature of the corpus in patients with no history of eradication, indicating an extended period after *H. pylori* elimination in these individuals. Subsequently, we compared patients with no history of eradication (group A) with those who underwent eradication therapy over five years previously (group E). In addition to being older and having a higher prevalence of elevated gastric cancer, open-type atrophy was also more prevalent in group A than in group B. One probable explanation for this discrepancy is that group A had a longer period before *H. pylori* eradication than group E. Another hypothesis proposed that groups A and B had distinct pathophysiological mechanisms, as evidenced by the fact that glandular atrophy and intestinal metaplasia typically show endoscopic and histological improvements long after eradication therapy (22, 23).

Group A comprised a heterogeneous population, including patients who inadvertently underwent eradication therapy due to the administration of antibiotics for non-*H. pylori*-related ailments, individuals who had unintentionally forgotten their history of *H. pylori* eradication, and those who experienced spontaneous elimination of *H. pylori* as a result of severe gastric mucosal atrophy. In this study, group D (O-2

Table 6. Comparison of Clinicopathological Characteristics between Patients with Severe Atrophy with Eradication History [Group B (O-2, O-3)] and Patients with Severe Atrophy and No Eradication (Group D).

	B: severe atrophy with eradication history (n=81)	D: severe atrophy with no eradication (n=56)	p value
Age mean age±SD	72±7.6	74±8.6	0.08
Male gender, n (%)	62 (76.5)	45 (80.4)	0.59
Location of U+M, n (%)	62 (76.5)	38 (67.9)	0.26
Elevated type, n (%)	13 (16.0)	22 (39.3)	0.002
Well differentiated type, n (%)	71 (87.7)	48 (85.7)	0.74
Sm, n (%)	15 (18.5)	12 (21.4)	0.67

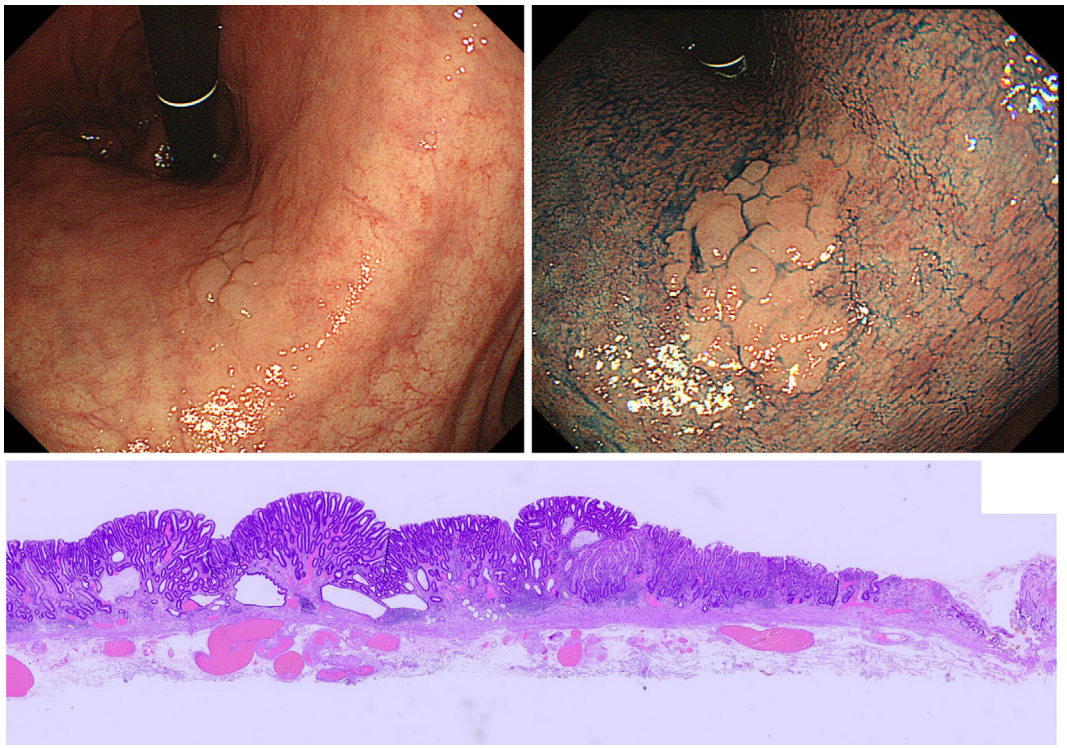

Figure 2. Gastric cancers in patients with previous *H. pylori* infection with no history of eradication therapy.

or O-3 atrophy) could be regarded as cases of pure spontaneous elimination of *H. pylori*. We performed a subgroup analysis between groups D and B (after eradication therapy); however, the results were the same as those of the analysis of group A vs. B or group A vs. E. Further research is required to understand the natural progression and underlying pathophysiology of gastric mucosal atrophy in patients with no history of eradication therapy.

An important finding of this study is that the spontaneous eradication group had a greater risk of developing elevated gastric cancer. Ito et al. found a significant elevation in serum gastrin levels among patients with elevated tumors compared with the gastrin levels among those with depressed tumors (24). The progression of gastric atrophy is widely known to diminish gastric acid secretion, leading to hypoacidity and subsequent hypergastrinemia, and gastrin exerts trophic effects on the gastric mucosa (25). In the present study, the elevated type tended to be more prevalent in group D (O-2 or O-3 atrophy) than group B. Therefore, we hypothesized that although gastrin levels were not measured in the enrolled patients, the progression of severe gastric mucosal atrophy and hypoacidity contributed to hypergastrinemia, thereby fostering the development of elevated gastric cancer.

In cases with severe gastric mucosal atrophy regardless of *H. pylori* eradication, elevated-type lesions might be easier to detect endoscopically. To match the background gastric mucosa, we performed a sub-analysis between patients with severe atrophy in group B (O-2, O-3) and group D, finding that group D showed a higher incidence of elevated gastric cancer than group B. Therefore, we consider elevated gastric cancer to be a potential characteristic of early gastric cancer in patients with a history of *H. pylori* infection with no history of eradication therapy.

In the present study, AIG was identified in 4 of the 60 patients (6.7%) with severe atrophy and no history of eradication therapy. Recent investigations have revealed a higher occurrence of elevated-type morphology and localization in the upper regions of gastric cancer in patients with AIG than in those without AIG (26, 27). We observed a higher incidence of elevated cancer and a propensity for cancer localization in the upper two-thirds of patients with no history of eradication therapy, similar to AIG-associated gastric cancer. Consequently, endoscopists should exercise vigilance in identifying elevated cancer in the upper regions of the stomach during esophagogastroduodenoscopy, although the underlying mechanisms of these similarities require further investigation. Given the typically elevated serum gastrin levels in patients with AIG (26, 27), hypergastrinemia may explain these similarities.

Several limitations associated with the present study warrant mention. First, it was a retrospective cohort study conducted at a single center, which might have introduced potential biases. Of the 102 patients in group A, we could not precisely detect the number of patients who had unintentionally forgotten their history of *H. pylori* eradication, and such cases could not be completely excluded from group A. However, we performed a medical consultation for each patient as thoroughly as possible regarding the eradication history. Therefore, we assume that the actual number of such cases is relatively small. Second, negativity for *H. pylori* was confirmed with antibody and histology; however, the 13C-urea breath test or stool antigen test could not be performed. Third, an immunostaining analysis was performed only in a select group of patients (group D); this might have resulted in incomplete exclusion of AIG and potentially led to an underestimation of AIG prevalence. However, we confirmed that corpus-dominant atrophy and antrum preservation were not observed in the remaining patients through endoscopic and histological analyses. Finally, serum gastrin levels were not measured, thus limiting further investigation and discussion of the possible pathophysiology underlying the relationship between the degree of atrophy and the location and morphology of gastric cancer.

In this study, we demonstrated that gastric cancer in patients with gastric atrophy and no history of eradication was associated with older age and a higher frequency of elevated morphology than in those with a history of eradication. Therefore, gastric cancer surveillance should be implemented in older patients with gastric atrophy and no history of eradication therapy. Endoscopists should be vigilant in detecting elevated gastric cancer in this particular population.

The authors state that they have no Conflict of Interest (COI).

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