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【 CASE REPORT 】

Helicobacter pylori-negative Gastric Adenocarcinoma Mimicking Verrucous Gastritis in the Antrum: A Case Report and Literature Review

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Abstract:

A 46-year-old man was referred to our hospital for the examination of a flat elevated lesion with an erosion-like depression, located on the greater curvature of the antrum. Endoscopic submucosal dissection was performed. Histological findings of the resected specimen demonstrated a well-differentiated tubular adenocarcinoma with a diameter of 12 mm. No atrophy was observed in the tumor-adjacent mucosa. Serum *Helicobacter pylori* antibody estimation and ^{13}C-urea breath tests yielded negative results. Immunohistochemical staining was positive for both gastric mucin and intestinal mucin. The final diagnosis was well-differentiated tubular adenocarcinoma with a gastrointestinal phenotype that originated in mucosa uninfected by *H. pylori*.

Key words: *Helicobacter pylori*-negative, gastrointestinal phenotype, differentiated gastric adenocarcinoma

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Introduction

The incidence of *Helicobacter pylori*-negative gastric cancer (HPNGC) is reported to be 0.42-0.66% (1, 2). The most common types of HPNGC are signet-ring cell carcinoma and adenocarcinoma of the fundic gland. More recently, rare cases of differentiated adenocarcinoma without *H. pylori* infection have been reported in the gastric antrum (3-17). The carcinogenic process of this type of cancer is suspected to be different from that of gastric cancer in *H. pylori*-infected gastritis. However, the detailed carcinogenetic process and clinicopathological characteristics of these lesions remain unclear.

We herein report a case of early gastric adenocarcinoma with a gastrointestinal phenotype and without *H. pylori* infection arising in the antrum.

Case Report

A 46-year-old man was referred to our hospital for a further examination and treatment. Six years earlier, a flat elevated lesion in the antrum had been identified during a routine endoscopic examination. The lesion did not change in size or morphology over time. The biopsy specimen revealed an adenoma of the intestinal type. He had no significant history of taking drugs, alcohol or smoking, and his family history was unremarkable. Serum *H. pylori* antibody and ^{13}C-urea breath tests and a histological examination were negative. *H. pylori* eradication therapy was not provided at that time, nor were proton-pump inhibitors or antibiotics prescribed at the time of the diagnosis of infection.

At our hospital esophagogastroduodenoscopy (EGD) showed a moderately reddish, single, flat elevated lesion with two humps and an erosion-like depression 10 mm in diameter mimicking verrucous gastritis on the greater curvature of the antrum, (Fig. 1A, B). No atrophy was observed

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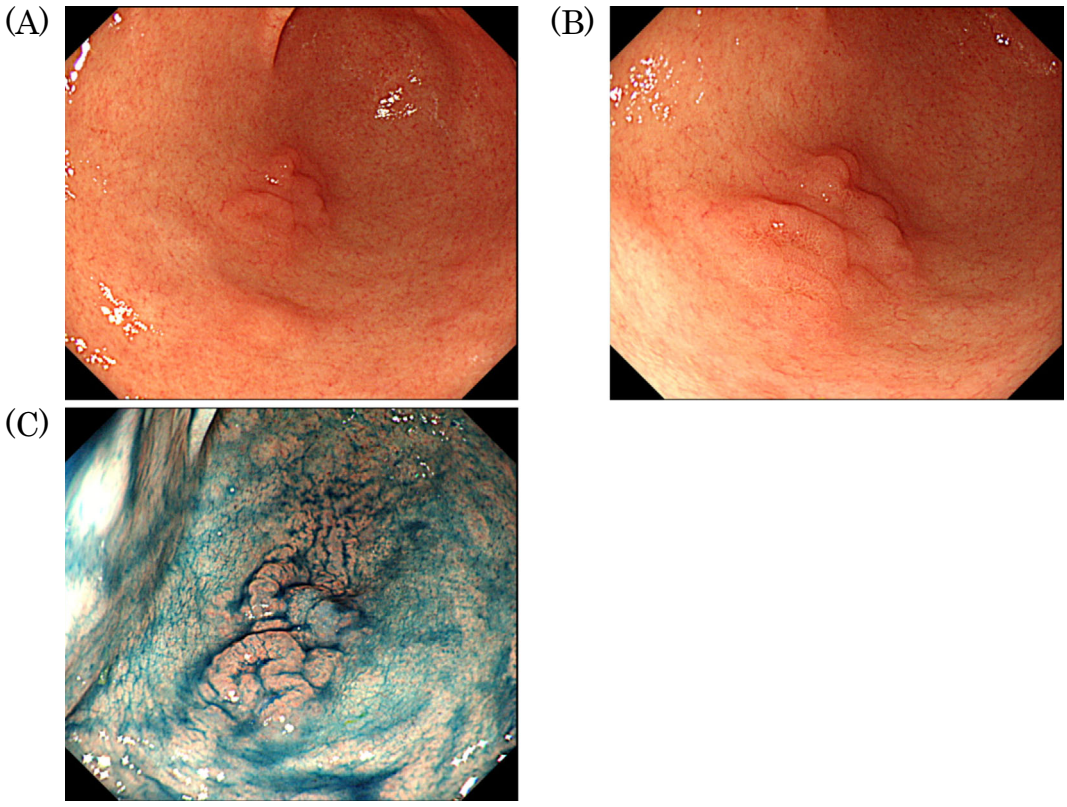

Figure 1. **Esophagogastroduodenoscopy showed a moderately reddish, single, flat elevated lesion with two humps and an erosion-like depression 10 mm in diameter mimicking verrucous gastritis on the greater curvature of the antrum. No atrophy was observed in the tumor-adjacent mucosa (A, B). Chromoendoscopy with indigo carmine clearly revealed the tumor area (C).**

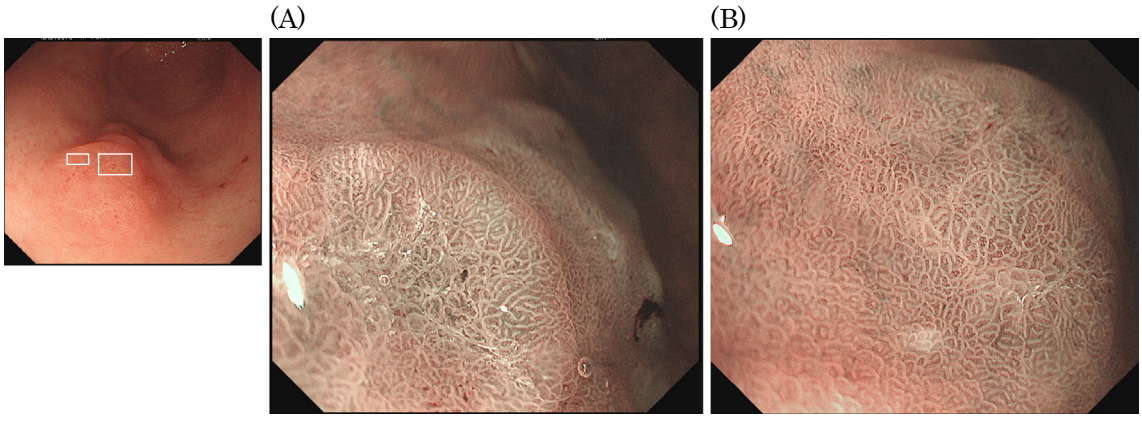

Figure 2. **Magnifying endoscopy with narrow-band imaging (ME-NBI) revealed a slightly irregular microsurface pattern and an irregular microvascular pattern with an unclear demarcation line (A: left square, B: right square).**

in the tumor-adjacent mucosa. Chromoendoscopy with indigo carmine clearly revealed the tumor area (Fig. 1C). Magnifying endoscopy with narrow-band imaging (ME-NBI) revealed a slightly irregular micro surface pattern and a microvascular pattern with an unclear demarcation line (Fig. 2).

We performed endoscopic submucosal resection on suspicion of adenocarcinoma (Fig. 3). A histopathological analysis revealed that the well-differentiated tubular adenocarcinoma was confined to the mucosa of the depressed area (Fig. 4A, B, Fig. 5). There was a fibromuscular obliteration without an adenocarcinoma in the pyloric side of the flat elevated lesions indicated by chromoendoscopy with indigo carmine (Fig. 4C).

Immunohistochemical staining demonstrated that the tumor cells were positive for CD10, MUC2, MUC5AC, and MUC6 (Fig. 6). These results suggested that the tumor cells were characteristic of the gastrointestinal phenotype. The final histopathological diagnosis was a well-differentiated tubular adenocarcinoma with a gastrointestinal phenotype that

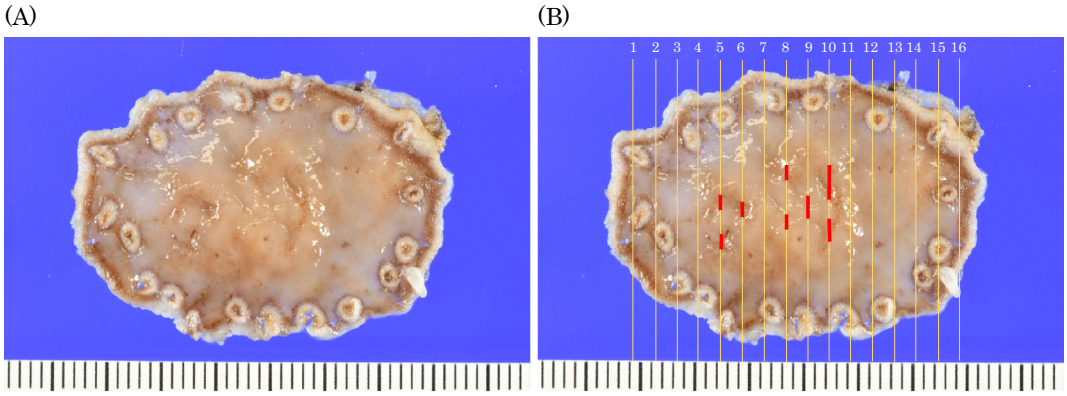

Figure 3. **Histopathological mapping of the resected specimen (A). The red line indicates tubular adenocarcinoma (B).**

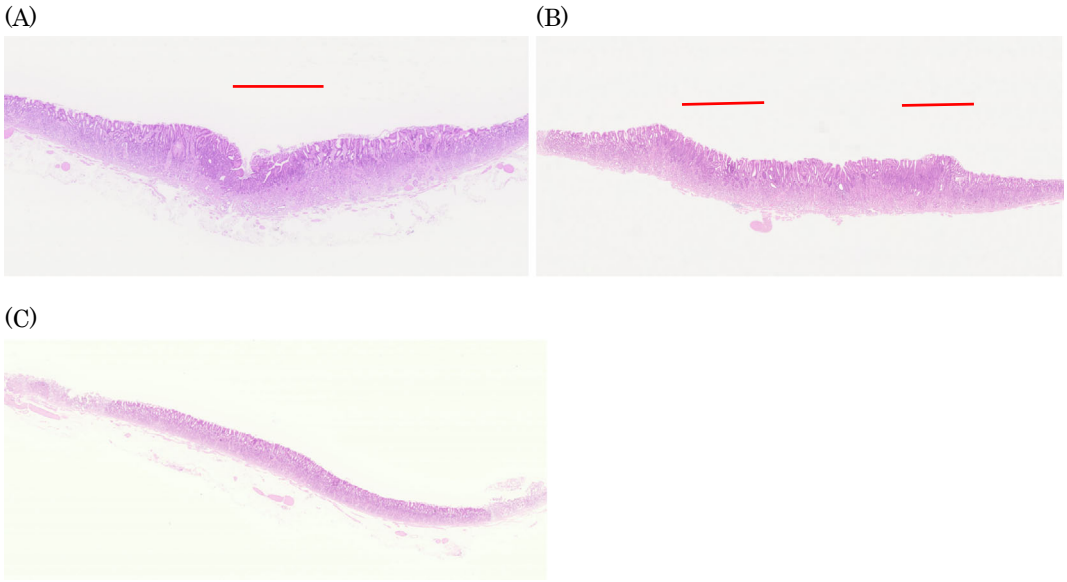

Figure 4. **Hematoxylin and Eosin staining. A histopathological analysis revealed that the well-differentiated tubular adenocarcinoma was confined to the mucosa of the depressed area. The lesions are the histopathological mapping of No.6 (A), No.10 (B) and No.12 (C).**

originated in *H. pylori*-uninfected mucosa.

Discussion

The incidence of HPNGC is reported to be 0.42-0.66% (1, 2). The most common types of HPNGC are signet-ring cell carcinoma and adenocarcinoma of the fundic gland. Differentiated tubular adenocarcinomas without *H. pylori* infection arising in the gastric antrum are rare. Since the determination of *H. pylori* infection is affected by false negatives in each examination, the diagnostic criteria for absence of *H. pylori* infection have not yet been clearly established. In our case, serum *H. pylori* antibody, ^{13}C-urea breath test, and a histological examination were negative; there was no history of *H. pylori* eradication; and there were no atrophic changes in the gastric mucosa. These met the minimum criteria for the absence of *H. pylori* infection of the stomach, as recommended by Yamamoto et al. (18). Furthermore, no risk factors for gastric cancer, such as type A gastritis, Epstein-Barr (EB) virus infection, genetic factors, or postoperative gastritis, were present.

In recent years, there have been 30 reported cases of differentiated adenocarcinoma arising in the antrum in the absence of *H. pylor*i infection (Table) (3-17). The percentage of men was 56%, and the mean age was 54 (range 30-73) years old. The lesions mainly occurred at different locations of the greater curvature. Morphologically, they were flat elevated or depressed lesions mimicking verrucous gastritis. The median tumor diameter was 7.6 (range 2-18) mm. The postoperative diagnosis was well-differentiated adenocarcinoma in all cases, and the depth was intramucosal, except in one case. None of the patients had lymphovascular invasion. The phenotypes included 16 cases of the intestinal phenotype, 11 of the gastrointestinal phenotype, and 3 of the gastric phenotype. None of the patients had a medical history or family history of gastric cancer. Little information is

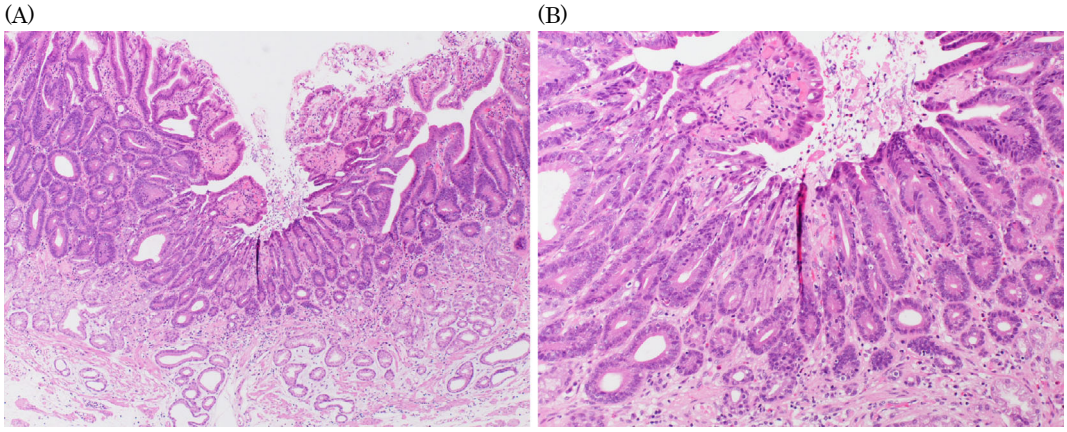

Figure 5. **Hematoxylin and Eosin staining. (A) Low-power field, (B) High-power field.**

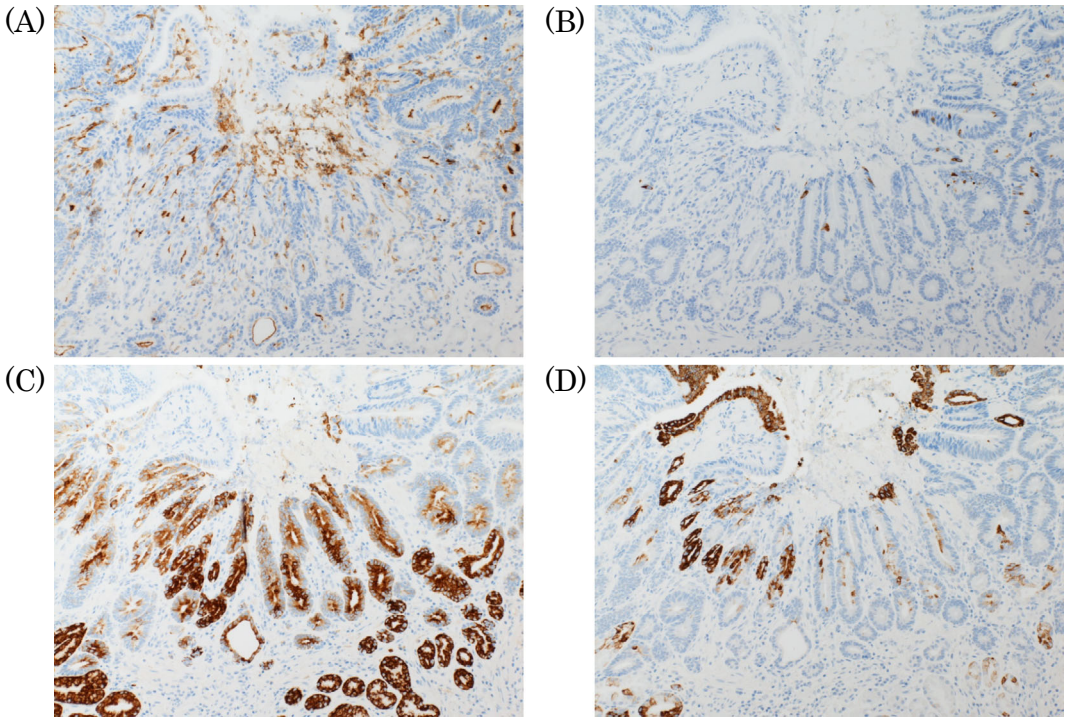

Figure 6. **Immunohistochemical staining demonstrated that the tumor cells were positive for CD10 (A), MUC2 (B), MUC5AC (C), and MUC6 (D).**

available concerning these patients' drinking and smoking habits or body mass index.

Takita et al. reported nine cases of single erosion with white-light endoscopy (17). Sato et al. reported that the intestinal phenotype was characterized by a macroscopic type resembling a single verrucous erosion found in the antrum (16). Using ME-NBI, Takita et al. reported cases in which the border, surface structure, and vascular structure atypia of the tumor were indistinct (17). Conversely, Kotani et al. reported that ME-NBI could distinguish differentiated tubular adenocarcinoma from surrounding erosions (5). Wada et al. reported that the tumor border, surface structure, and vascular structure became clear after the administration of antacids (15, 19). Our patient had received no antacids. Esophagogastroduodenoscopy (EGD) showed a single, flat elevated lesion with two humps. Histological mapping showed non-tumor mucosa intervening in the tumor of two depressed areas. We did not perform multiple biopsies in the past, and the non-tumor mucosa intervening in the tumor was not a scar by a biopsy. While previous reports demonstrated a wide range of characteristics, we hope that an appropriate diagnostic method will be developed in the future.

Our case occurred in *H. pylori*-uninfected gastric mucosa without atrophy and intestinal metaplasia, which occurred through a mechanism different from that of conventional gastric cancer; however, the process has not been elucidated. Tatsugami et al. reported the role of bile acid reflux in the stomach as a carcinogenic mechanism (20). Of the 22 previously reported cases, 11 were located in the greater curvature, which is normally more exposed to bile acids (21).

Table. A Summary of Previous Case Reports with Differentiated Adenocarcinoma Arising in the Antrum without *Helicobacter pylori* Infection.

No.	Reference	Age	Gender	Location	Morphology	Size (mm)	Preoperative diagnosis	Differentiation	Depth	Phenotype	Lymphovascular invasion	VS classification system		Metaplasia
1	3	73	Female	N/D	IIa	4	N/D	tub1	M	Gastric	0	N/D	N/D	N/D
2	4	30s	Female	Gre	IIc	6	Group 5	tub1	M	Intestinal	0	DL+	MS irreg./ MV irreg.	0
3	5	67	Male	Post	IIc	8	Group 3	tub1	M	Intestinal	0	DL+	MS irreg./ MV reg.	0
4	6	30s	Female	Ant	IIa+IIc	11	Group 4	tub1	M	Gastrointestinal	0	DL+	MS reg./ MV reg.	1
5	7	70s	Female	Gre	IIa+IIc	10	Group 5	tub1	M	Gastrointestinal	0	DL+	MS irreg./ MV irreg.	0
6	8	54	Male	Gre	IIa	13	N/D	tub1	M	Gastrointestinal	0	DL+	MS irreg./ MV reg.	0
7	9	40	Male	Less	IIa	9	Group 3-4	tub1	M	Intestinal	0	DL+	MS irreg./ MV irreg.	0
8	10	68	Male	Post	IIc	Multiple	Group 5	tub1	M	Intestinal	0	Unclear	MS irreg./ MV irreg.	1
9	11	40s	Male	Ant	IIa	2	Group 5	tub1	M	Gastric	0	Unclear	MS irreg./ MV irreg.	0
10		60s	Female	Ant	IIa	3	Group 5	tub1	M	Gastric	0	DL+	MS irreg./ MV irreg.	0
11	12	60s	Female	Gre	IIc	6	Group 5	tub1	M	Intestinal	0	DL+	MS irreg./ MV irreg.	0
12	13	40	Male	Gre	IIc	10	Group 5	tub1	M	Gastrointestinal	0	DL+	MS irreg./ MV irreg.	1
13	14	34	Male	Post	IIa+IIc	9	Group 3	tub1	M	Intestinal	0	DL+	MS irreg./ MV irreg.	0
14	15	70	Female	Gre	IIa+IIc	6	Group 3	tub1	M	Gastrointestinal	0	DL+	MS irreg./ MV irreg.	0
15	16	66	Male	N/D	IIc	9	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
16		49	Male	N/D	IIc	5	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
17		65	Female	N/D	IIa	3	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
18		61	Female	N/D	IIc	5	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
19		43	Female	N/D	IIc	3	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
20		48	Male	N/D	IIa	7	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
21		52	Female	N/D	IIa	5	N/D	tub1	M	Intestinal	0	N/D	N/D	N/D
22	17	51	Male	Less	IIa+IIc	10	Group 4	tub1	M	Intestinal	0	N/D	N/D	N/D
23		57	Male	Ant	IIa	6	Group 3	tub1	M	Intestinal	0	N/D	N/D	N/D
24		56	Male	Post	IIa	12	Group 2	tub1	M	Intestinal	0	N/D	N/D	N/D
25		51	Male	Gre	IIa	14	Group 3	tub1	M	Gastrointestinal	0	N/D	N/D	N/D
26		32	Male	Gre	IIa	8	Group 5	tub1	M	Gastrointestinal	0	N/D	N/D	N/D
27		48	Female	Gre	IIa	10	Group 3	tub1	M	Gastrointestinal	0	N/D	N/D	0
28		61	Female	Gre	IIa+IIc	18	Group 5	tub1	SM1	Gastrointestinal	0	N/D	N/D	N/D
29		64	Male	Post	IIa	2	Group 2	tub1	M	Gastrointestinal	0	N/D	N/D	N/D
30		64	Male	Gre	IIa	3	Group 5	tub1	M	Gastrointestinal	0	N/D	N/D	N/D
31	Our case	46	Male	Gre	IIc	12	Group 3	tub1	M	Gastrointestinal	0	Unclear	MS irreg./ MV irreg.	0

Matsuhisa et al. reported that gastric mucosa uninfected by *H. pylori* occasionally accompanies intestinal metaplasia, in the presence of increased concentrations of bile acid in the stomach (22). Kishimoto et al. reported multiple intestinal-type gastric cancers arising from the non-atrophic gastric mucosa with sporadic intestinal metaplasia (11). Bile acid is a well-known carcinogen, and reflux may induce sporadic intestinal metaplasia in the pyloric glands in the absence of *H. pylori* infection (23).

However, Takita et al. conversely reported that all patients

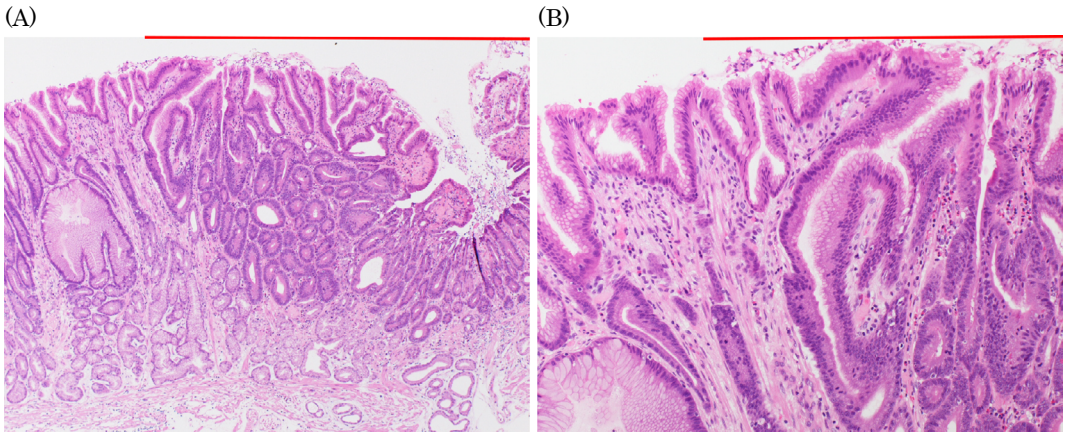

Figure 7. Fibromuscular obliteration of the lamina propria was observed in the background mucosa. (A) Low-power field, (B) High-power field.

had fibromuscular obliteration of the lamina around the lesion, similar to mucosal prolapse syndrome (MPS) (9, 12, 24). Our case also showed fibromuscular obliteration surrounded by noncancerous mucosa. (Fig. 7A, B). MPS causes chronic mechanical stimulation and is histologically characterized by fibromuscular obliteration, but there are few reports of complications with cancer. Yamamoto et al. reported a case of MPS complicated by adenocarcinoma after long-term follow-up by colonoscopy, suggesting the possibility of carcinogenesis due to chronic inflammation (25). In our case, there is a possibility that carcinogenesis occurred in the protuberant part that caused fibromuscular obliteration due to physical stimulation by peristalsis. Furthermore, the two cancers may have developed simultaneously in a multicentric manner. Since these cancers occurs in area affected by physical stimulation by peristalsis and bile acids reflex, we speculated that both should be involved in carcinogenesis. Our lesion occurred in areas that were strongly affected by peristaltic stimulation and bile acids. However, the relationship between these chronic stimulations and carcinogenic mechanisms is still unclear.

This case was an extremely well-differentiated adenocarcinoma with a gastrointestinal phenotype (26). In general, it has been reported that the superficial elevated type of gastric cancer is mostly intramucosal with low atypia and shows very slow growth. Most previous reports concerned intramucosal cancer, except for one case, and lymphovascular invasion was not confirmed in any cases. However, it is difficult to detect such lesions, since they often have non-neoplastic epithelium inside the lesion, as in gastric cancers detected after *H. pylori* eradication (11, 18).

The histological features of this phenotype may be useful for the tumor diagnosis, although the further accumulation of cases is necessary. Thus far, it has been difficult to diagnose cancer using only biopsy specimens. Therefore, it is necessary to work closely with a pathologist to make an accurate diagnosis.

Conclusion

We reported a case of *H. pylori*-negative gastric adenocarcinoma with a gastrointestinal phenotype arising in the antrum. The incidence of HPNGC may increase in the future with the decline in *H. pylori* infection, making it essential that we fully understand the endoscopic findings and characteristics of HPNGC arising in the antrum.

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

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