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A Case of Gastric Adenocarcinoma of Fundic Gland Mucosa Type Arising from *Helicobacter pylori*-Negative Mucosa

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Abstract

An 80-year-old woman was referred to our hospital with a gastric depressed lesion identified by esophagogastroduodenoscopy（EGD）screening. EGD revealed a depressed lesion of approximately 5 mm in size at the great curvature of the gastric upper body. Magnifying endoscopy with narrow band imaging revealed irregularly circular marginal crypt epithelium with irregular vessels in the circular intervening part. Histopathological examination of biopsy specimens revealed a well differentiated tubular adenocarcinoma with low-grade atypia, pure gastric type. The patient was negative for *Helicobacter pylori*（*H. pylori*）infection as determined by anti-*H. pylori* immunoglobulin G antibody. We performed endoscopic submucosal dissection, and the tumor was successfully removed en bloc. Histopathological diagnosis of the resected specimen was gastric adenocarcinoma of fundic gland mucosa type（GA-FGM）（3×3 mm in size, tub1, pT1a（M）, ly0, v0, pUL0, pHM0, pVM0）indicated that the resection was curative. GA-FGM is a rare gastric adenocarcinoma composed of atypical cells with differentiation toward the fundic gland as well as the foveolar epithelium.

Key words : Gastric cancer, *Helicobacter pylori*, Magnifying endoscopy, Endoscopic submucosal dissection

Introduction

Gastric adenocarcinoma of fundic gland type（GA-FG）was reported as a new variant of gastric adenocarcinoma in 2010[1)]. GA-FG is defined as a well differentiated adenocarcinoma with chief cell differentiation and is positive for pepsinogen-I, a marker of chief cells[1)2)]. The tumor cells of GA-FG develop from the deep layer of the lamina propria, which is covered with normal foveolar epithelium[3)]. GA-FG is generally thought to develop in non-atrophic mucosa in *Helicobacter pylori*（*H. pylori*）-negative or -eradicated patients[4)]. Recently, Tanabe et al. reported that gastric adenocarcinoma of fundic gland mucosa type（GA-FGM）exhibited a phenotype that included atypical cells with differentiation towards the fundic gland as well as the foveolar epithelium[5)]. However, the endoscopic features of GA-FGM remain unclear. We herein report a case of GA-FGM arising from *H. pylori*-negative mucosa.

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Case Report

An 80-year-old woman was referred to our hospital with a gastric depressed lesion identified by esophagogastroduodenoscopy (EGD) screening. She had a medical history of breast cancer, which completely remitted by mastectomy and chemotherapy 6 years ago. She had no drinking and smoking career. She had no family history of cancer. EGD revealed a depressed lesion of approximately 5 mm in size at the great curvature of the gastric upper body (Fig.1a, b). Magnifying endoscopy with narrow band imaging (ME-NBI) revealed irregularly circular marginal crypt epithelium with irregular vessels in the circular intervening part. A demarcation line was noted around the depressed lesion (Fig.2). Histopathological examination of biopsy specimens revealed a well differentiated tubular adenocarci-

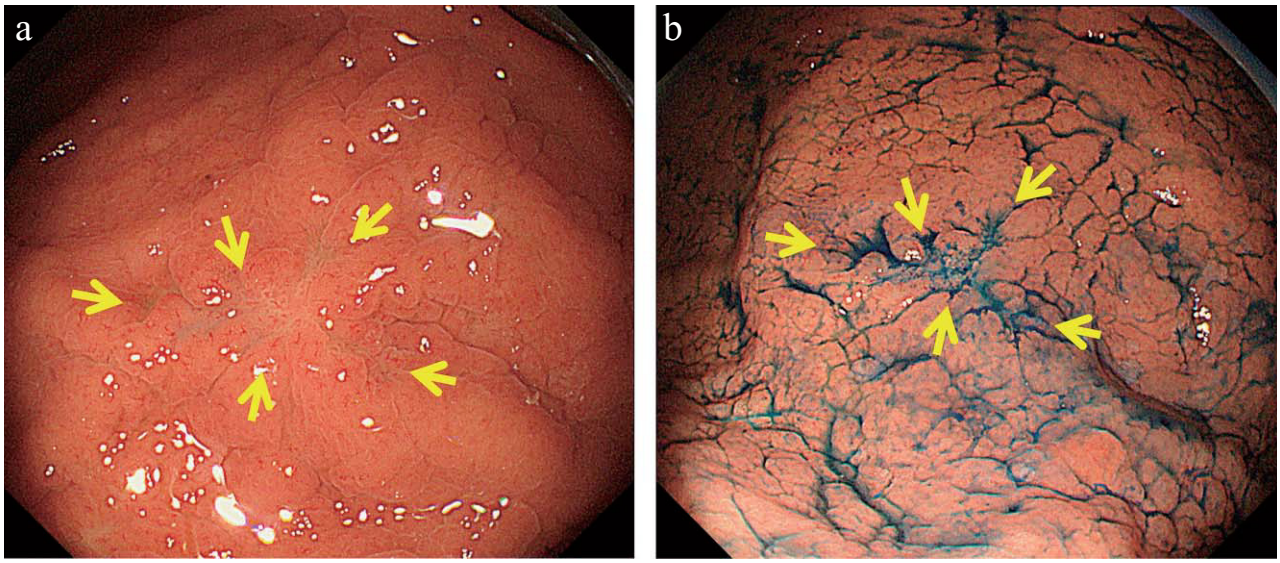

Figure 1. Findings of upper gastrointestinal endoscopy. Endoscopic view showing a small depressed lesion (arrows) of approximately 5 mm in size in the upper portion of the gastric body. a. White light image. b. Indigo carmine spraying image.

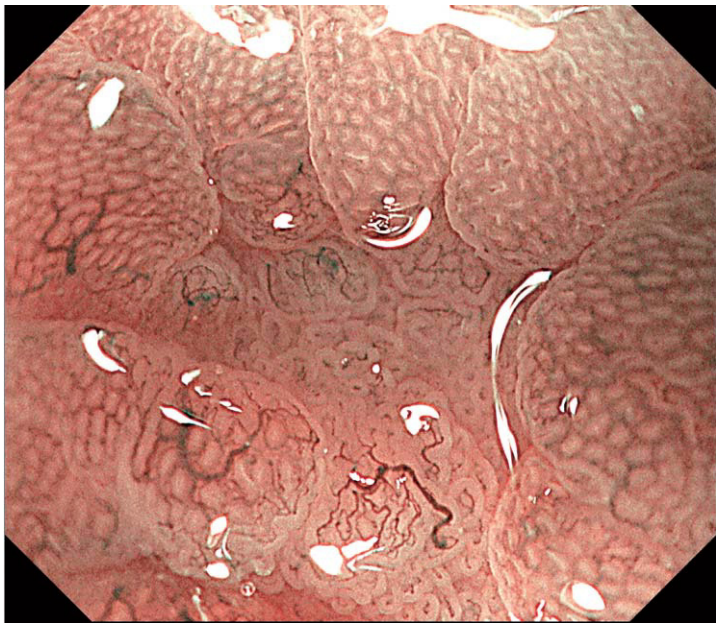

Figure 2. Findings of magnifying endoscopy with narrow band imaging. Magnifying endoscopy with narrow band imaging showing an irregular microvascular pattern and an irregular microsurface pattern with a demarcation line.

noma with low-grade atypia, pure gastric type（Fig.3）. Based on these endoscopic and histopathological findings, we diagnosed this lesion to be an early-stage type 0-IIc differentiated adenocarcinoma that was limited to the mucosa. The background mucosa of the lesion was endoscopically- and histopathologically-free of mucosal atrophy and the patient was found to be negative for *H. pylori* by anti-*H. pylori* immunoglobulin G antibody detection（serum level, 3 U/mL）. We performed endoscopic submucosal dissection（ESD）, and the tumor was successfully removed en bloc. The ESD specimen showed a slightly depressed lesion measuring 5×3 mm（Fig.4）. Histopathological examination of the resected specimen revealed a well differentiated tubular adenocarcinoma with gland architecture similar to the chief cell-like and parietal cell-like columnar cells. The tumor was localized in the mucosal layer and most of the tumor surface was covered with atypical foveolar epithe-

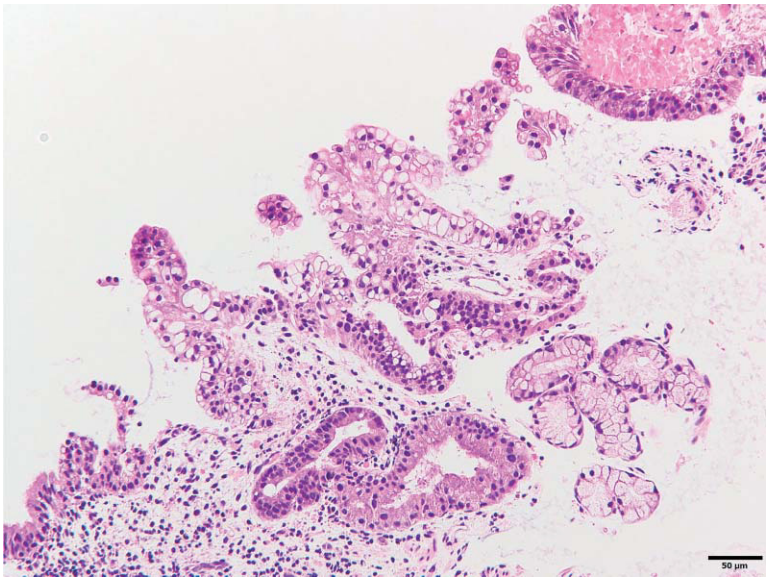

Figure 3. Histopathological findings of a forceps biopsy specimen from the gastric depressed lesion. The gastric biopsy specimen showing a well differentiated tubular adenocarcinoma with low-grade atypia, pure gastric type（hematoxylin-eosin stain）.

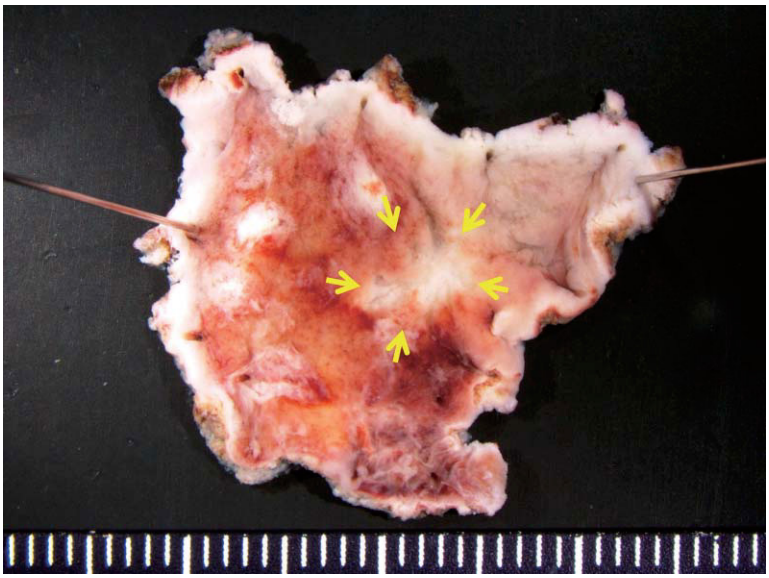

Figure 4. Macroscopic findings of the resected gastric specimen by ESD. The resected gastric specimen showing a locally-whiteish depressed lesion（arrows）of 5×3 mm in diameter.

lium（Fig.5a, b）. The depth of tumor invasion was intramucosal carcinoma, and neither lymphatic nor venous invasion was recognized. No ulcer scar was detected in any sections. Both the horizontal and vertical margins were free from carcinoma. Immunohistochemical analysis revealed that the tumor cells were positive for MUC5AC, MUC6, pepsinogen-I, and H^+/K^+-ATPase（Fig.5c, d, e, f）. The final histopathological diagnosis was GA-FGM（3×3 mm in size, tub1, pT1a（M）, ly0, v0, pUL0, pHM0, pVM0）, indicating that the resec-

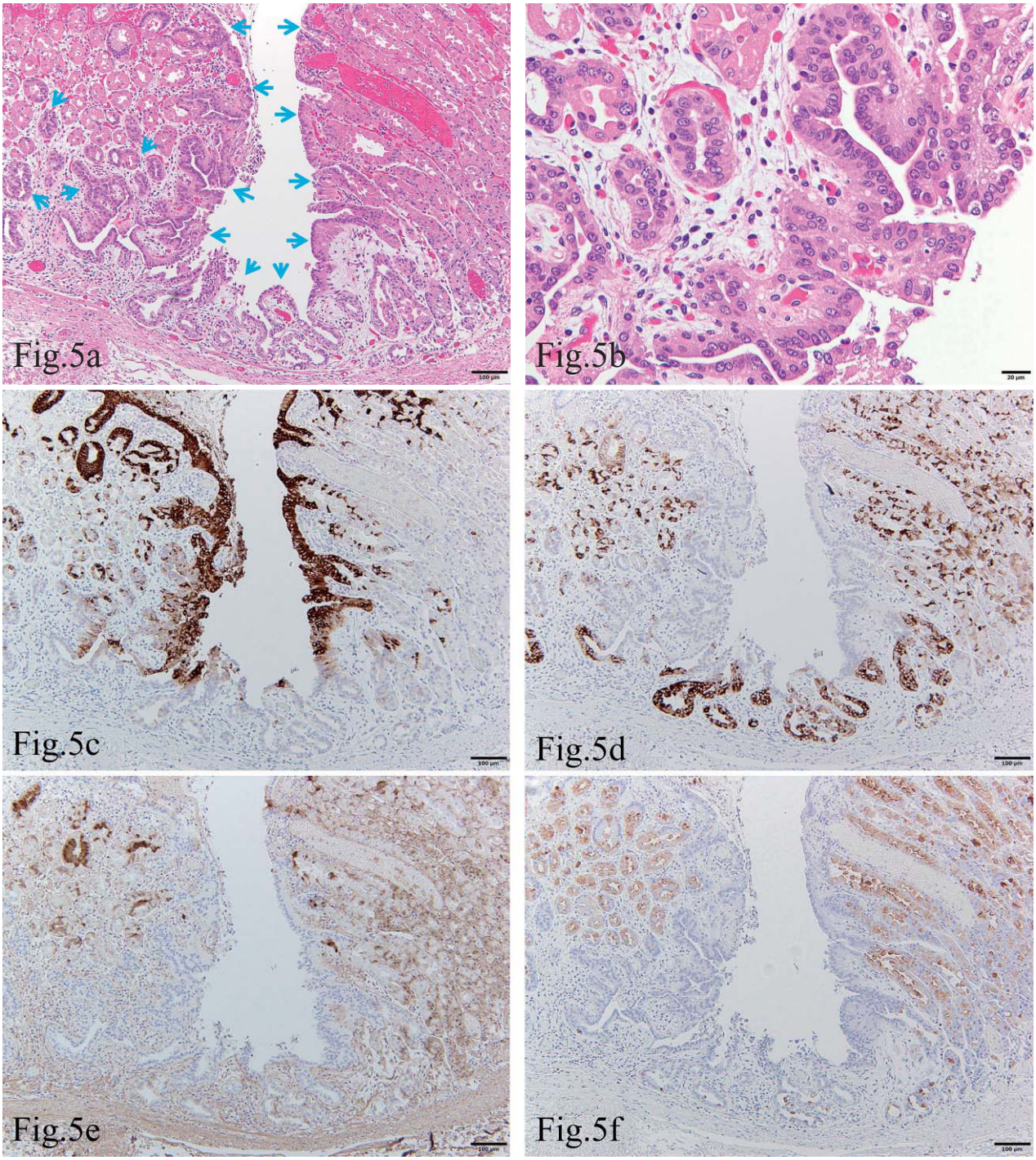

Figure 5. Histopathological findings and immunohistochemical analysis of the resected gastric specimen by ESD. a. The resected gastric specimen showing a well differentiated tubular adenocarcinoma（arrows）with gland architecture mimicking fundic gland.（hematoxylin-eosin stain） b. The resected gastric specimen showing the tumor restricted to the mucosal layer and most of the tumor surface covered with atypical foveolar epithelia（arrows）.（hematoxylin-eosin stain）c, d, e, f. Immunohistochemical analysis. The tumor cells are positive for c. MUC5AC, d. MUC6, e. pepsinogen-I, and f. H^+/K^+-ATPase.

tion was curative. The patient continues to be monitored by endoscopic study and has not shown tumor recurrence or evidence of any other gastric cancer.

Discussion

GA−FG is proposed as a new histological type of gastric cancer manifesting with differentiation towards the fundic gland[1]. GA−FG commonly occurs in the upper portion of the stomach and is derived from the deep part of the normal fundic gland with non−atrophic mucosa in *H. pylori*−negative patients[4]. The most common endoscopic findings of GA−FG are reported to be a submucosal tumor shape that is whiteish in color, exhibiting dilated blood vessels with branching architecture[2], and with even small lesions having invaded to the submucosa[4]. Immunohistochemically, scattered positivity for H^+/K^+−ATPase was observed in addition to pepsinogen−I and MUC6 expression. Recently, Tanabe et al. reported that gastric adenocarcinomas that differentiate into carcinoma of the fundic gland can be broadly categorized as GA−FG and GA−FGM. GA−FG has been reported to be a well differentiated adenocarcinoma with mainly chief cell−dominant type, which is covered with normal foveolar epithelium. On the other hand, GA−FGM has been reported to be a well differentiated adenocarcinoma with mucous neck cell−dominant type or chief−mucous−neck−combination type, which is covered to be atypical foveolar epithelium[5]. Cases of GA−FGM are mainly submucosally−invasive, with average tumor diameters that are larger than those of GA−FG[5]. The growth of GA−FGM is rapid[5][6]. However, the endoscopic features of GA−FGM remain unclear.

Eleven cases of GA−FGM including our case were reported from 2010 to 2018（Table 1）. These included six male and five female patients（mean age, 70.3 years）. All cases of GA−FGM were detected in the upper third of the stomach. The macroscopic type mainly consisted of elevated lesions（0−IIa, five lesions；0−IIa＋IIc, three lesions；0−I＋IIa, one lesion）, and there were only two depressed lesions（0−IIc）. The mean size of the lesions was 6.6 mm. The depth of invasion of gastric carcinoma included mainly submucosally−invasive carcinoma in nine lesions, and intramucosal carcinoma in only two lesions including our case. The mean sizes of submucosally−invasive carcinoma and intramucosal carcinoma were 7.2 mm and 4 mm, respectively. Even small lesions of less than 10 mm exhibit invasion to the submucosa in GA−FGM, and thus the depth of invasion should always be carefully examined in suspected cases. ME−NBI revealed irregular microvascular patterns（MVP）and/or irregular microsurface patterns（MSP）with demarcation lines in six cases including our case. Six cases were diagnosed as gastric cancer based on the features of vessels and crypt structures using ME−NBI. ME−NBI assessment is based on the worldwide standard diagnostic system of the VS（vessel plus surface）classification, which uses MVP and MSP[7]. Previous reports indicated the difficulty of diagnosing GA−FG by ME−NBI, because the tumor cells of GA−FG develop from the deep layer of the lamina propria, which is covered with normal foveolar epithelium[4]. However, GA−

Table 1. Clinical characteristics of 11 reported cases of GA−FGM including our case.

	Age	Gender	Location	Macroscopic type	Size（mm）	Invasive depth	VS classification	*H. pylori* infection	Treatment	References
1	54	M	U	0−IIa＋IIc	6	SM	N/A	N/A	ESD	5
2	67	F	U	0−IIa	7	SM	IMSP	Negative	ESD	5
3	74	M	U	0−IIa	5	SM	N/A	N/A	ESD	5
4	66	M	U	0−IIc	6	SM	N/A	Negative	ESD	5
5	60	M	U	0−IIa＋IIc	9	SM	N/A	Negative	ESD	5
6	67	F	U	0−IIa	6	SM	N/A	N/A	ESD	5
7	74	M	U	0−IIa	4	SM	IMVP＋RMSP	Negative	ESD	8
8	68	F	U	0−IIa	7	SM	IMVP＋IMSP	Negative	ESD	8
9	87	M	U	0−I（＋IIa）	3（15）	M	IMVP＋IMSP	Positive	ESD	9
10	70	F	U	0−IIa＋IIc	15	SM	IMVP＋IMSP	Positive	ESD, Ope	6
11	88	F	U	0−IIc	5	M	IMVP＋IMSP	Negative	ESD	Our case

U, upper third of the stomach；VS classification, vessel plus surface classification；IMVP, irregular microvascular pattern；IMSP, irregular microsurface pattern；RMSP, regular microsurface pattern；*H. pylori*, *Helicobacter pylori*；N/A, not available；Ope, operation

FGM tumor cells are exposed on the surface of the epithelia, thereby allowing for a diagnosis by ME-NBI[8)9)]. In our case, ME-NBI was useful for the diagnosis of GA-FGM because the tumor cells were exposed on the surface of the epithelia. Six cases were negative for *H. pylori* infection, and two cases were positive. In our *H. pylori*-negative patient, the lesion was localized in the mucosal layer with non-atrophic mucosa. Even in the absence of atrophic mucosa due to *H. pylori* infection, if a lesion with the above-described endoscopic characteristics is recognized, detailed examination should be performed in cases that suspect GA-FGM.

In conclusion, we experienced a rare case of early gastric adenocarcinoma that was recently categorized as GA-FGM. We summarized 11 reported cases of GA-FGM and discussed their characteristics in context with previous reports. When examining patients we need to bear in mind the possibility of GA-FGM originating from *H. pylori*-negative gastric mucosa. Given the sparsity of reported GA-FGM cases, it is necessary to accumulate more endoscopic data to identify the characteristics of GA-FGM.

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Conflicts of interest

The authors declare no conflicts of interest.

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（令和 1. 9. 2受付，令和 1.10.10受理）

「The authors declare no conflict of interest.」