ABSTRACT

Gastric adenocarcinoma of the fundic gland mucosa type (GA-FGM) was proposed as a new variant of gastric adenocarcinoma of the fundic gland type (GA-FG). However, at present, the influence of Helicobacter pylori and the speed of progression and degree of malignancy in GA-FGM remain unclear. Herein, we report the first case of intramucosal GA-FGM that was endoscopically observed before and after H. pylori eradication over 15 years. The lesion showed the same tumor size with no submucosal invasion and a low MIB-1 labeling index 15 years after its detection using endoscopy. The endoscopic morphology changed from 0-IIa before H. pylori eradication to 0-IIa+IIc and then 0-I after H. pylori eradication. These findings suggest that the unaltered tumor size reflects low-grade malignancy and slow growth, and that the endoscopic morphology is influenced by H. pylori eradication.

Keywords: GA-FGM; Gastric adenocarcinoma of fundic gland type; GA-FG; Helicobacter pylori; Eradication

INTRODUCTION

Gastric adenocarcinoma of the fundic gland type (GA-FG) is defined as a well-differentiated adenocarcinoma with fundic gland differentiation, confirmed by immunohistochemical staining with pepsinogen I and H’/K’ ATPase [1]. The atypical cells of GA-FG are localized to the deep layer of the gastric mucosa, and the surface of GA-FG is covered by non-cancerous foveolar epithelium [2]. Reflecting the pathological features, the morphology typically presents as a submucosal tumor on conventional endoscopy, with a regular microsurface pattern without a demarcation line on magnifying endoscopy with narrow-band imaging (ME-NBI) [3]. GA-FG reportedly shows low-grade malignancy and slow growth [2]. Submucosal invasion is observed in 60% of GA-FG cases, and advanced GA-FG is extremely rare [2,4]. Singhi et al. [5] proposed changing the descriptive term from GA-FG to oxyntic
Long-term Observation of GA-FGM

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Gastric adenocarcinoma of the fundic gland mucosa type (GA-FGM) was proposed as a new variant of GA-FG in 2015 by Tanabe et al. [6]. GA-FGM shows atypical cells with differentiation towards the fundic gland as well as the foveolar epithelium, as confirmed by immunohistochemical staining for MUC5AC, as well as pepsinogen I and/or H+/K+ ATPase. The surface of the GA-FGM is covered by atypical cells with foveolar differentiation; therefore, ME-NBI might be able to observe the irregularity of the microsurface [7]. GA-FGM is expected to show more aggressive growth than GA-FG, as it shows more varied differentiation than GA-FG, and most of the initially reported cases have exhibited invasion of the deep submucosal layer [6]. However, several cases of intramucosal GA-FGM have been reported recently [8-12]; therefore, the degree of malignancy of GA-FGM is controversial at present. In addition, it is unclear whether Helicobacter pylori infection or its eradication influences the morphology of GA-FGM.

Herein, we report the first case of intramucosal GA-FGM that was endoscopically observed before and after H. pylori eradication over 15 years.

CASE REPORT

A 71-year-old man underwent esophagogastroduodenoscopy (EGD) during a medical checkup. Endoscopic examination showed a slightly reddish and flat elevated lesion on the greater curvature of the gastric upper body (Fig. 1), although the histological findings of the specimens obtained by an endoscopic biopsy showed a non-neoplastic change. During the medical checkup, the patient underwent EGD 8 times without biopsy, and the endoscopic morphology was unchanged before H. pylori eradication. He then received H. pylori eradication therapy due to a history of H. pylori-associated gastritis 10 years after the first endoscopy. Endoscopy after H. pylori eradication revealed a depressed area at the center of the tumor that corresponded to 0-IIa+IIc based on the Paris classification (Fig. 2). After...
H. pylori eradication, he underwent EGD 5 times and 1 biopsy, resulting in the diagnosis of a non-neoplastic lesion.

Fifteen years after the first endoscopy, he was referred to our institution for endoscopic submucosal dissection (ESD) of the gastric lesion because the lesion was suspected to be a malignant tumor due to morphological change. Physical examination revealed no abnormal findings. The patient’s blood test results were within normal limits, including carcinoembryonic antigen and cytokeratin 19 fragment levels. The patient was negative for serum immunoglobulin G antibody and stool antigen for H. pylori because of his history of H. pylori eradication. Computed tomography showed no evidence of lymph node metastasis. EGD showed a reddish and protruding lesion, which was classified as type 0-I (Fig. 3A). Chromoendoscopy revealed a roughly villous structure and a well-demarcated line around the 0-I lesion (Fig. 3B). ME-NBI showed a microsurface pattern of irregular villous and partially absent structures with a demarcation line and microvascular pattern of an irregular network (Fig. 3C). Based on these endoscopic findings, we diagnosed the tumor as an intramucosal well-differentiated adenocarcinoma and successfully removed the tumor en bloc using ESD.

**Fig. 2.** Endoscopic findings after H. pylori eradication. The lesion has a depressed area at the center of the tumor, which was classified as 0-IIa+IIc after H. pylori eradication (A). Chromoendoscopy shows a clear depressed lesion and well-demarcated line around the 0-IIa lesion (B).

**Fig. 3.** Endoscopic findings before endoscopic submucosal dissection. Esophagogastroduodenoscopy shows a reddish and protruding lesion that was classified as type 0-I (A). Chromoendoscopy shows a roughly villous structure and well-demarcated line around the 0-I lesion (B). Magnifying endoscopy with narrow-band imaging shows a microsurface pattern of an irregularly villous and partially absent structure with a demarcation line and a microvascular structure of an irregular network pattern (C).
Regarding the histological findings, hematoxylin and eosin staining revealed an irregularly shaped tubular structure resembling the fundic gland and foveolar epithelium with no submucosal or lymphovascular invasion (Fig. 4A). The tumor surface was covered with atypical foveolar epithelium with mitotic figures on a high-power view (Fig. 4B). On immunohistochemistry, pepsinogen-I, MUC6, and H’/K’ ATPase, which indicate differentiation toward the fundic gland (chief cells, mucous neck cells, and parietal cells), and MUC5AC, which indicates differentiation toward foveolar epithelium, were positive in the tumor cells (Fig. 4C-F). The MIB-1 labeling index (MIB-1 LI) was 5.1% (Fig. 4G). As a result, the lesion was diagnosed as intramucosal GA-FGM. The patient was discharged 5 days after treatment with no complications.

DISCUSSION

This is the first case of GA-FGM that was endoscopically observed for over 15 years. The lesion size did not change during the long observation period, and the invasion depth remained at the mucosal layer. Ogasawara et al. [13] observed a GA-FGM for 8 years and reported that the lesion remained a submucosal cancer of the same size. Sato et al. [14] also showed that a GA-FGM remained a submucosal cancer of the same size for 5 years after its detection. These findings suggest that GA-FGM with no change in tumor size has a low invasive ability and slow growth.

We also showed that the endoscopic morphology changed from 0-IIa before H. pylori eradication to 0-IIa+IIc and then 0-I after H. pylori eradication. This lesion did not show any morphological changes over 10 years, from the first biopsy to H. pylori eradication. Similar to our case, 2 cases of GA-FGMs with no intervention for H. pylori reportedly showed no morphological changes in their long-term course [13,14]. Our case showed a depressed area at the center of the tumor only after H. pylori eradication. This depressed site was not thought to have been influenced by the endoscopic biopsy because it had been 10 years since...
the biopsy. The morphology of early gastric cancer reportedly shifts from an elevated type to a depressed type following *H. pylori* eradication in the short term \([15,16]\). In addition, *H. pylori* eradication has been known to decrease the thickness of the covering layer over tumor ducts in GA-FG \([17]\). No cases concerning the morphological changes of GA-FG without *H. pylori* eradication have been reported. Our findings suggest that *H. pylori* eradication changed the morphology of GA-FGM from the flat elevated type to depressed type, similar to the situation with conventional gastric adenocarcinoma and GA-FG. Five years after *H. pylori* eradication, the lesion lost its depressed site and again was a protruding type. Early gastric cancers more than 36 months after *H. pylori* eradication reportedly tend to show a reversal in their morphology and proliferative activity \([15]\). In this case, the effects of *H. pylori* eradication seemed to be lost over a long period, resulting in the covering layer of GA-FGM thickening. This is the first report of long-term sequential changes in GA-FGM morphology on endoscopy after *H. pylori* eradication.

Including the present case, 29 cases of GA-FGMs have been reported from 2015 to 2021 \([6,14,18-21]\) (Table 1). This study included 18 men and 11 women. Seventeen cases were negative for *H. pylori* infection, 2 were positive, and 4 had previously been positive. Twenty-four lesions were detected in the upper third of the stomach, and none were detected in the lower third. Excluding cases without individual data, the median tumor size with intramucosal invasion and submucosal invasion was 5 mm (range: 3–6 mm) and 7 mm (range: 4–23 mm), respectively. According to the Paris classification, 4 lesions were morphologically classified as polypoid type (0-I), 20 as non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc), 3 as mixed type (0-IIa+IIc, 0-I+IIa), and 2 as submucosal tumor shape. Before endoscopic or surgical treatment, only one of the 8 lesions was diagnosed as GA-FGM using biopsy specimens. In contrast, 18 of 20 lesions were diagnosed as gastric cancer using ME-NBI according to the magnifying endoscopy simple diagnostic algorithm for early gastric cancer, suggesting that it is worthwhile to perform diagnostic ESD for histologically non-neoplastic lesions when the lesions are suspected to be cancerous on ME-NBI. With regard to invasive depth, 9 lesions (31%) were intramucosal and 20 (69%) were submucosal. We recognize that 2

| Author            | Cases | OP (yr) | Age (yr) | Sex (M:F) | Hp infection (P:N:N/A) | Location (U:M:L) | Size (mm) | Macroscopic type | Histology of biopsy | MESDA-G (cancer:non cancer) | Invasive depth (M:SM) | ESD/Ope |
|-------------------|-------|---------|----------|-----------|------------------------|------------------|-----------|------------------|---------------------|------------------------|----------------------|---------|
| Tanabe et al. \[6\] | 6     | N/A     | 65 (54–74) | 4:2 | 0:3:3 | 6:0:0 | 6.5 (5–9) | 0-IIa, 3, Ila 1, Ila+Iic 2 | N/A | N/A | 0:6 | 6:0 |
| Fujiwara et al. \[7\] | 2     | N/A | 71 (68–74) | 1:1 | 0:2:0 | 2:0:0 | 5.5 (4–7) | Ila 2 | N/A | 2:0 | 0:2 | 2:0 |
| Takahashi et al. \[8\] | 1     | N/A | 87 | M | Positive | M | 3 | 0-I (+Ila) | Group 3 | IMVP+IMSP | M | ESD |
| Yaita et al. \[9\] | 1     | N/A | 60s | M | Previous | M | 6 | 0-Ila | N/A | IMVP+AMSP | M | ESD |
| Kumei et al. \[18\] | 1     | N/A | 70s | F | Positive | U | 15 | SMT | GA-FGM | IMVP+IMSP | SM | ESD |
| Uchida et al. \[19\] | 1     | N/A | 70s | M | N/A | M | 23 | SMT | N/A | N/A | N/A | ESD+TG |
| Ogasawara et al. \[1\] | 1     | 8 | 70s | M | Previous | U | 10 | 0-Iic | N/A | IMVP+IMSP | SM | ESD |
| Miyajima et al. \[20\] | 1     | N/A | 40s | F | Previous | U | 8 | 0-Ila | Group 3 | N/A | SM | ESD |
| Ikeda et al. \[10\] | 1     | N/A | 40s | M | Negative | U | 5 | 0-I | Group 2 | IMVP+IMSP | M | ESD |
| Ishibashi et al. \[11\] | 1     | N/A | 88 | F | Negative | U | 5 | 0-Ila | Tub 1 | IMVP+IMSP | M | ESD |
| Imamura et al. \[21\] | 10    | N/A | 68 (32–81) | 5:5 | 0:10:0 | 9:1 | 7.7 (4–15) | 0-I 2, Ila 7, Iib 1 | N/A | 9:1 | 3:7 | N/A |
| Kojima et al. \[12\] | 1     | N/A | 40s | M | Negative | U | 7 | 0-Ila | Group 2 | RMSP+AMVP | M | ESD |
| Sato et al. \[14\] | 1     | 5 | 70s | M | Negative | U | 8.5 | 0-I | Non neoplastic | N/A | N/A | N/A |
| Our case          | 1     | 15 | 71 | M | Previous | M | 5 | 0-Ila | Group 1 | IMVP+IMSP | M | ESD |

Table 1. Reported cases of gastric adenocarcinoma of the fundic gland mucosa type

OP = observation period; HP = *Helicobacter pylori*; MESDA-G = magnifying endoscopy simple diagnostic algorithm for early gastric cancer; N/A = not available; SMT = submucosal tumor; IMVP = irregular microvascular pattern; IMSP = irregular microsurface pattern; AMSP = absent microsurface pattern; AMVP = absent microvascular pattern; RMSP = regular microsurface pattern; TG = total gastrectomy; ESD = endoscopic submucosal dissection; GA-FGM = gastric adenocarcinoma of the fundic gland mucosa type; Sex (M = male; F = female); Hp infection (P = positive; N = negative); Location (U = upper part; M = middle part; L = lower part); Invasive depth (M = intramucosal; SM = submucosal); Ope = operation.
lesions reported as advanced GA-FG with subserosal invasion may have been GA-FGM based on a review of the mucin phenotype [22,23]. The sizes of the 2 lesions were 44 mm and 47 mm, respectively, which were significantly larger than those of intramucosal and submucosal GA-FGMs (P<0.05). Thus, most GA-FGMs maintained intramucosal or submucosal invasion and showed slow growth, similar to GA-FG; however, cases with an increased tumor size might show more aggressive growth, similar to conventional gastric adenocarcinomas.

In conclusion, the present case showed the history of a patient with a tumor of stable size with no submucosal invasion and a low MIB-1 LI 15 years after its detection by endoscopy, illustrating low-grade malignancy and slow growth. However, the degree of malignancy of GA-FG might increase with tumor size. *H. pylori* eradication may influence the endoscopic morphology of GA-FGM in the clinical setting. The accumulation of similar cases will help clarify the influence of *H. pylori* and the phenotype of GA-FGM with aggressive growth.

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