

## Gastric adenocarcinoma of fundic gland type spreading to heterotopic gastric glands

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### Abstract

Herein, we present a case of gastric adenocarcinoma of fundic gland type (GA-FG) spreading to heterotopic gastric glands (HGG) in the submucosa. A 58-year-old man with epigastric pain was referred to our hospital and underwent an esophagogastroduodenoscopy. A Borrmann type II gastric cancer at the antrum and a 10 mm submucosal tumor-like lesion in the lesser curvature of the upper third of the stomach were detected. Histological examination of the biopsy specimens obtained from the submucosal tumor-like lesion suggested a GA-FG. Therefore, endoscopic submucosal dissection was performed as excisional biopsy, and histopathological examination of the resected specimen confirmed a GA-FG and HGG proximal to the GA-FG. Although the GA-FG invaded the submucosal layer slightly, the submucosal lesion of the GA-FG had a poor stromal reaction and was located just above the HGG in the submucosa. Therefore, we

finally diagnosed the lesion as a GA-FG invading the submucosal layer by spreading to HGG.

**Key words:** Gastric adenocarcinoma of fundic gland type; Heterotopic gastric glands; Endoscopic submucosal dissection; Paracancerous lesion; Pepsinogen-I; H/K-ATPase

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**Core tip:** A 58-year-old man had a 10mm submucosal tumor-like lesion in the lesser curvature of the upper third of the stomach. Histological examination of the biopsy specimens suggested a gastric adenocarcinoma of fundic gland type (GA-FG), therefore, endoscopic submucosal dissection was performed as excisional biopsy. Histopathological examination of the resected specimen confirmed a GA-FG invading the submucosal layer slightly, and heterotopic gastric glands (HGG) proximal to the GA-FG. A GA-FG spreading to HGG in the submucosa was diagnosed because the submucosal lesion of the GA-FG had a poor stromal reaction and was located just above the HGG.

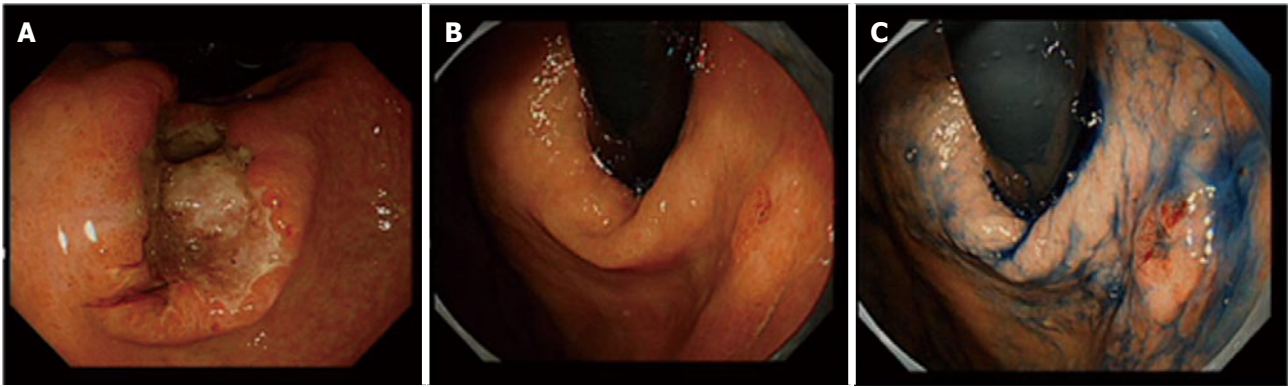
Manabe S, Mukaisho K, Yasuoka T, Usui F, Matsuyama T, Hirata I, Boku Y, Takahashi S. Gastric adenocarcinoma of fundic gland type spreading to heterotopic gastric glands. *World J Gastroenterol* 2017; 23(38): 7047-7053 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i38/7047.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i38.7047>

## INTRODUCTION

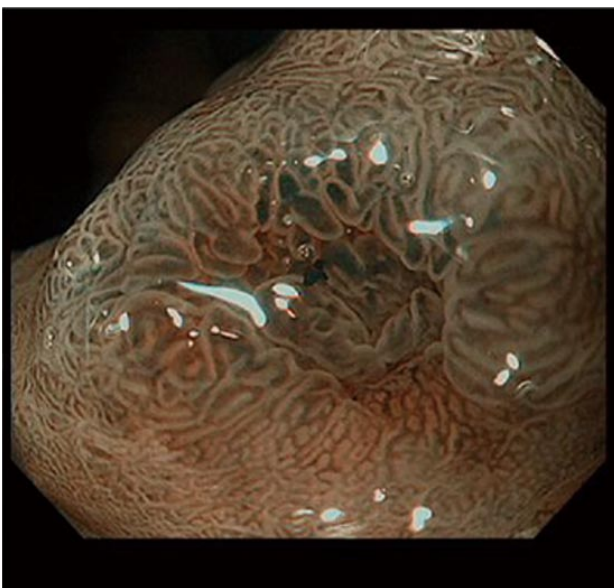
Gastric adenocarcinoma of fundic gland type (GA-FG) is a new histological type of gastric cancer proposed by Ueyama *et al.*<sup>[1]</sup> in 2010. As the concept of GA-FG has spread since then, new findings have been reported<sup>[2]</sup>. GA-FG tends to invade the submucosal layer while it is still small because it arises from the deep layer of the lamina propria mucosae<sup>[1]</sup>. On the other hand, heterotopic gastric glands (HGG) are regarded as paracancerous lesions<sup>[3,4]</sup>, and gastric cancers associated with HGG have been reported<sup>[5,6]</sup>. However, HGG are not considered to contribute to the development of GA-FG because the pathogenesis of GA-FG is different from that of the regular histological type of gastric cancer. We encountered a case of GA-FG suggested to have invaded the submucosal layer by spreading to HGG, which coincidentally existed proximal to the GA-FG. In addition to a GA-FG with a very rare mode of submucosal invasion, this case demonstrated the possibility of GA-FG arising from the gastric mucosa with atrophic change, provided there are remnant gastric fundic glands. Herein, we report this case with a brief review of the literature.

## CASE REPORT

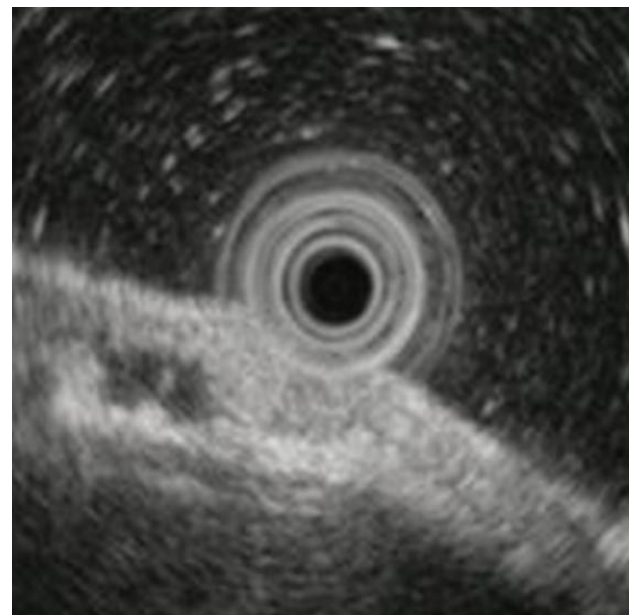
A 58-year-old man with epigastric pain was referred to our hospital. Esophagogastroduodenoscopy (EGD) revealed a Borrmann type II gastric cancer at the antrum (Figure 1A) and a 10 mm submucosal tumor-like lesion in the lesser curvature of the upper third of the stomach (Figure 1B and C). Atrophy of the gastric mucosa was classified as O-1 (according to the Kimura and Takemoto classification<sup>[7]</sup>), although the patient had undergone *Helicobacter pylori* (*H. pylori*) eradication therapy 4 years ago, and has not taken any proton pump inhibitors since then. Histological examination of the biopsy specimens obtained from the submucosal tumor-like lesion showed that the superficial area retained the normal foveolar epithelium. However, atypical cells mimicking fundic gland cells with mildly enlarged nuclei were observed in the deep layer of the lamina propria mucosae. These findings suggested a GA-FG. Narrow-band imaging with magnifying endoscopy (NBI-ME) performed later showed a regular microvascular pattern and a regular microsurface pattern according to the vessel plus surface classification system<sup>[8]</sup> with a concomitant depressed area at the center of the submucosal tumor-like lesion expected to be a biopsy scar (Figure 2). Endoscopic ultrasonography (EUS) findings revealed the tumor slightly invading the third layer and a hypoechoic mass located in the third layer near the tumor (Figure 3). Blood test findings revealed carcinoembryonic antigen level of 2.2 ng/mL and carbohydrate antigen 19-9 level of 14.3 U/mL, indicating that the tumor markers were within the normal range. Although gastric wall thickening due to the advanced gastric cancer at the antrum was seen on the abdominal CT scan, nodal or distant metastasis was absent. Based on the above findings, a partial gastrectomy was required for gastric cancer at the antrum. The submucosal tumor-like lesion in the lesser curvature of the upper third of the stomach was suspected to be a GA-FG; hence, we decided to perform endoscopic submucosal dissection (ESD) as excisional biopsy. Since histopathological findings of the ESD-resected specimen may indicate the need for an additional surgery, ESD was performed before surgery for the gastric cancer at the antrum, and en bloc resection was achieved. The ESD-resected specimen was 30 mm in diameter, whilst a 7 mm × 4 mm slightly elevated lesion was identified (Figure 4). Similar to the histological findings of the biopsy specimens, atypical cells mimicking fundic gland cells, mainly chief cells and partially parietal cells, with mildly enlarged nuclei were seen mainly in the deep layer of the lamina propria mucosae. The mucosal surface was covered completely with non-neoplastic foveolar epithelium; thus, the tumor was not exposed to the mucosal surface (Figure 5A).



**Figure 1 Esophagogastroduodenoscopy findings.** A: A Borrmann type II gastric cancer was detected at the antrum; B and C: A 10 mm submucosal tumor-like lesion on the lesser curvature of the upper third of the stomach was detected. Atrophic gastritis O-1 according to Kimura and Takemoto classification was recognized.



**Figure 2 Narrow-band imaging with magnifying endoscopy findings.** There were few irregularities in the microvessel architecture and microsurface structure. Therefore, we diagnosed a regular microvascular pattern and a regular microsurface pattern. The depressed area at the center was expected to be a biopsy scar.

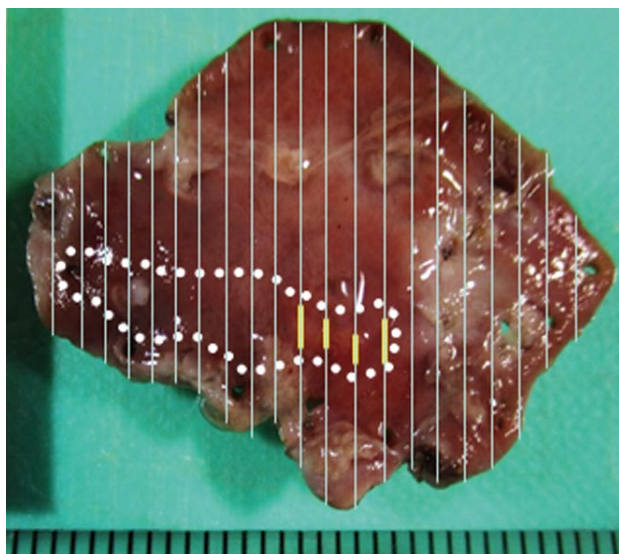


**Figure 3 Endoscopic ultrasonography findings.** The tumor slightly invaded the third layer, although it was located mainly in the second layer. Moreover, a hypoechoic mass located in the third layer near the tumor was detected.

Upon immunohistochemical examination, the tumor showed positivity for MUC6 and negativity for MUC2 and MUC5AC, indicating a gastric phenotype (Figure 5B-D). Moreover, diffuse positivity for pepsinogen-I and scattered positivity for H/K-ATPase was found, indicating a differentiation dominantly toward chief cells and focally toward parietal cells (Figure 5E and F). Although the lesion was located mainly in the deep layer of the lamina propria mucosae, it had partially invaded the submucosal layer up to 450  $\mu$ m. Furthermore, HGG were observed in the submucosal layer, proximal to the tumor. The submucosal lesion of the tumor had a poor stromal reaction and was located just above the HGG in the submucosa (Figure 6). Based on these findings, the final diagnosis was: U, Less, 30  $\times$  20 mm, type 0-IIa, 7  $\times$  4 mm, adenocarcinoma of fundic gland type, pT1b1 (450

$\mu$ m), UL (-), ly (-), v (-), pHM0, pVM0 (according to the Japanese classification of gastric carcinoma<sup>[9]</sup>). In addition, we have concluded that the GA-FG had invaded the submucosal layer by spreading to the HGG. After obtaining these results, we performed EUS again to examine the presence of other HGG. Thus, several hypoechoic masses considered to be HGG were seen in the entire stomach, and we diagnosed diffuse type HGG. A partial gastrectomy was required for the Borrmann type II gastric cancer at the antrum. Moreover, due to the high risk of cancer arising from the gastric remnant because of the diffuse type HGG, we performed a total gastrectomy upon the patient's request. After the total gastrectomy, the gastric cancer at the antrum was diagnosed as: L, Less, type 2, 40  $\times$  35 mm, pT3 (SS), intermediate type (int), INFa, ly2, v2, pN0, pPM0, pDM0 (according to the Japanese classification of gastric carcinoma<sup>[9]</sup>), and multiple





**Figure 4** Spread of the gastric adenocarcinoma of fundic gland type and heterotopic gastric glands mapped on the endoscopic submucosal dissection-resected specimen. Yellow line spread of the gastric adenocarcinoma of fundic gland type (GA-FG), White dotted line spread of heterotopic gastric glands (HGG). The endoscopic submucosal dissection -resected specimen was 30 mm × 20 mm in size. The tumor was slightly elevated and measured 7 mm × 4 mm. The GA-FG and HGG partially overlapped.

HGG in the entire stomach were confirmed. However, we could not find evidence of this cancer related to diffuse type HGG. In addition, considering the risk of multiple gastric cancers associated with diffuse type HGG, the entire stomach was examined histologically. In doing so, we detected an intramucosal cancer in the lesser curvature of the lower gastric body, which was not previously detected by endoscopy before surgery. Although there was no remnant GA-FG near the ESD ulcer scar, a distribution of HGG was seen.

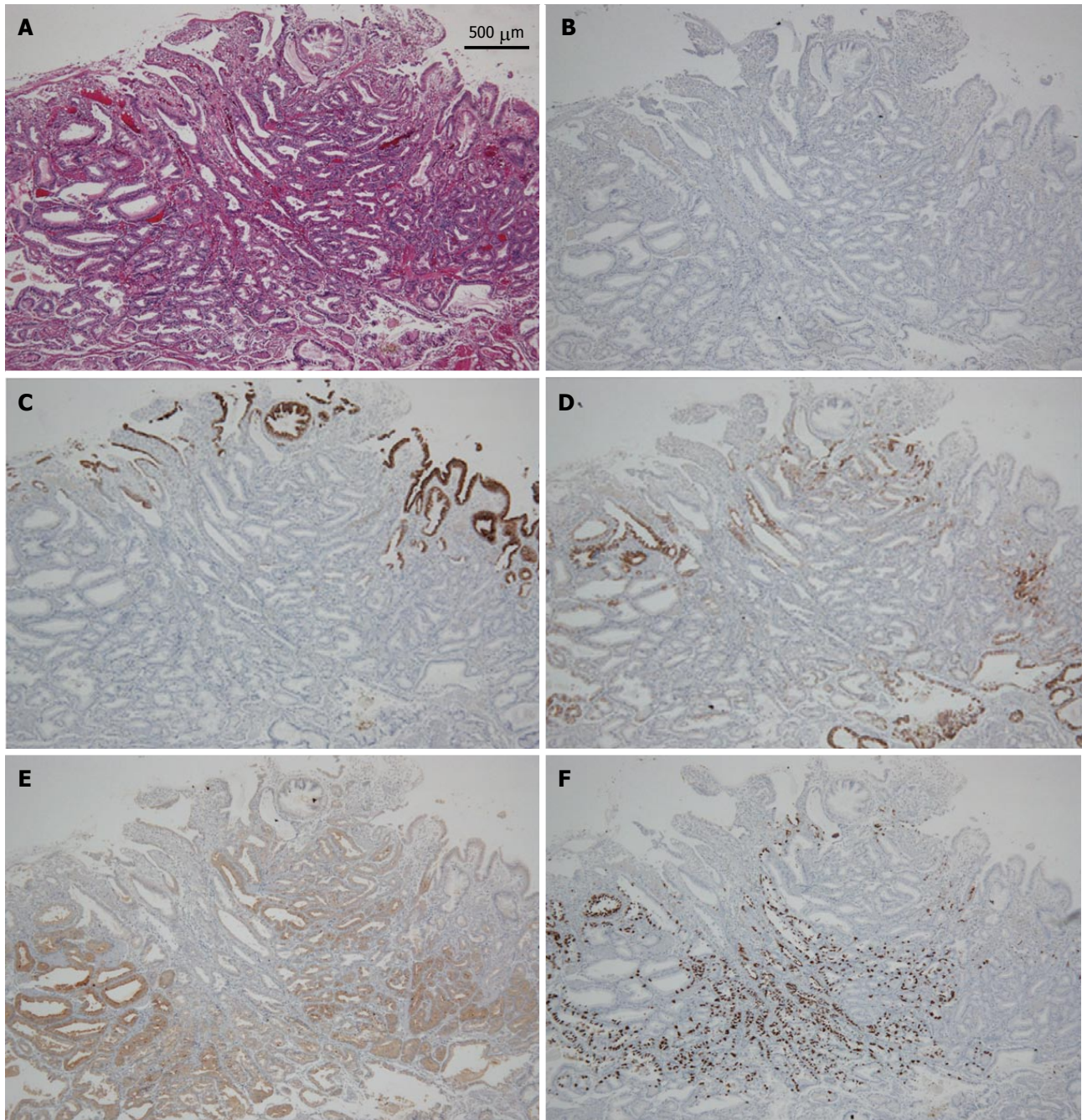
## DISCUSSION

GA-FG is a new histological type of gastric cancer<sup>[1]</sup>. According to Ueyama *et al.*<sup>[10]</sup>, endoscopic properties of GA-FG include no intestinal metaplasia or atrophic change in the surrounding mucosa, faded or whitish color, submucosal tumor shape with a soft appearance, and dilated vessels with branching architecture. Although the pathogenesis of GA-FG is unclear, GA-FG tends to arise from the normal gastric mucosa of the fundic gland region without atrophic change or intestinal metaplasia<sup>[2]</sup>. Therefore, *H. pylori* infection is not considered to contribute to the development of GA-FG, unlike for the regular histological type of gastric cancer.

On the other hand, HGG are gastric glands that are observed in the submucosa and are naturally seen in the lamina propria mucosae<sup>[3,4]</sup>. Clinically, HGG are regarded as paracancerous lesions and are associated with gastric cancer, particularly, multiple gastric cancers<sup>[3,4]</sup>. HGG are classified into 4 types based on

their number and range of distribution: solitary type with 3 sites or less, localized type with 4-9 sites at the focal area, broad type with 4-9 sites in the broad area, and diffuse type with at least 10 sites which exist in the entire stomach<sup>[4]</sup>. Of these, the diffuse type is seen in 98% of gastric cancer complications, and the rate of complication with multiple gastric cancers is reported to be 32%<sup>[3]</sup>. The association between HGG and gastric cancer is unclear. However, one dominant hypothesis is that both HGG and gastric cancer develop because of repeated erosion and regeneration of the mucosa, suggesting that HGG are paracancerous lesions<sup>[3,4]</sup>. Caution is required when performing EGD for patients with HGG, particularly diffuse type HGG, since there is the possibility that micro-gastric cancers that are difficult to detect endoscopically may be present. Indeed, as in our case, after total gastrectomy, histopathological examination revealed a micro-intramucosal cancer that was not detected endoscopically before surgery. There is no consensus on the treatment of HGG. As mentioned previously, because the rate of complication of gastric cancer is very high, particularly with diffuse type HGG, EGD must be conducted periodically with caution. In our case, in addition to the high risk of gastric cancer arising due to diffuse type HGG, a partial gastrectomy was required for the Borrmann type II gastric cancer at the antrum. Therefore, a total gastrectomy was performed upon the patient's request.

The GA-FG observed in our case presented a submucosal tumor shape, which corresponds to the endoscopic properties reported by Ueyama *et al.*<sup>[10]</sup>. A possible reason the GA-FG presented a submucosal tumor shape is that, in addition to the proliferation of tumor cells in the deep mucosal layer, the HGG were also present in the submucosa. Retrospectively, the hypoechoic mass near the GA-FG that was seen on EUS before ESD was suggested to be HGG. The ESD-resected specimen showed no tumor exposed to the mucosal surface; thus, NBI-ME showed a regular microvascular pattern and a regular microsurface pattern. Since GA-FG arises from the deep layer of the lamina propria mucosa, there is a high rate of submucosal invasion while the tumor diameter is small<sup>[1]</sup>. In our case also, the GA-FG invaded the submucosal layer up to 450  $\mu$ m. However, the submucosal lesion of the GA-FG had a poor stromal reaction and was located just above the HGG in the submucosa. Therefore, the GA-FG was considered to have invaded the submucosal layer by spreading to the HGG. There are a few case reports of regular histological type of gastric cancer spreading to HGG<sup>[11]</sup>. However, to the best of our knowledge, this is the first case of GA-FG spreading to HGG. Currently, in the Japanese classification of gastric carcinoma, there is no definition concerning the depth of tumor invasion that spreads to HGG in the submucosa<sup>[9]</sup>. However, since similarly, esophageal cancer with intraductal spreading is handled as intramucosal cancer as long as it is



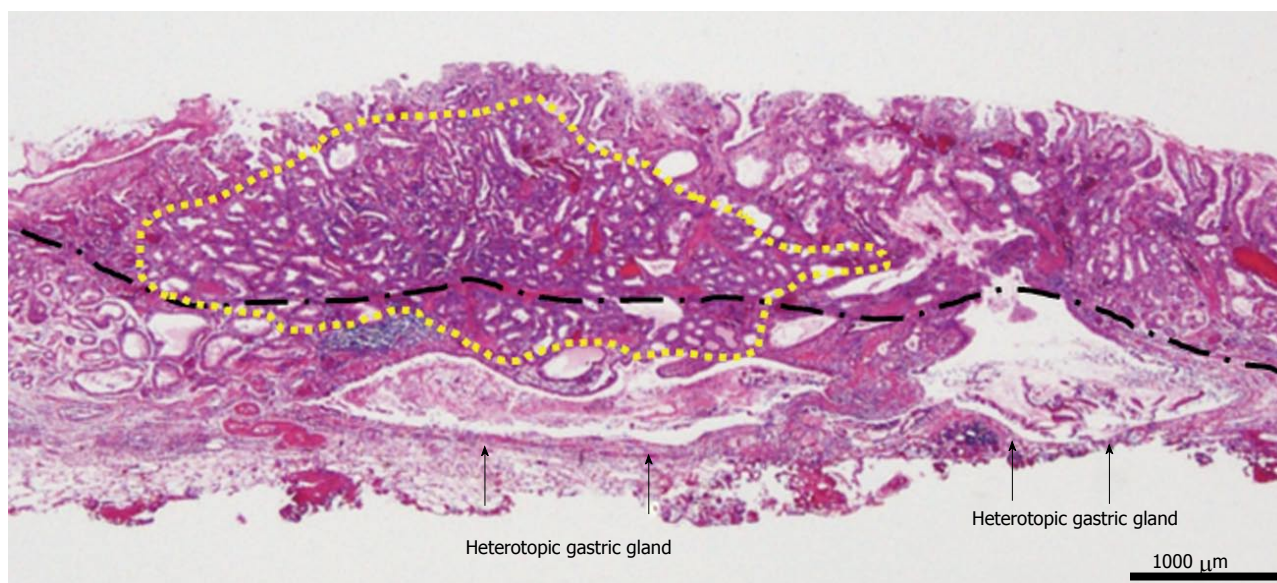
**Figure 5** Histopathological and immunohistochemical findings of the endoscopic submucosal dissection-resected specimen. A: H&E staining. There were atypical cells with mildly enlarged nuclei in the deep layer of the lamina propria mucosae. They mimicked fundic gland cells, mainly chief cells and partially parietal cells. The mucosal surface was covered completely with non-neoplastic foveolar epithelium; thus, the tumor was not exposed to the mucosal surface; B: MUC2 staining: almost negative; C: MUC5AC staining: almost negative except for normal superficial foveolar epithelium; D: MUC6 staining: partially positive and indicating a gastric phenotype; E: Pepsinogen staining: diffusely positive in the deep layer of the lamina propria mucosae, corresponding to gastric adenocarcinoma of fundic gland type, and indicating a differentiation toward chief cells; F: H/K-ATPase staining: scattered positive in the deep layer of the lamina propria mucosae, indicating a differentiation toward parietal cells focally.

retained in the esophageal proper glands<sup>[12]</sup>, gastric cancer spreading to HGG should likely be handled as intramucosal cancer<sup>[5,6]</sup>.

As mentioned earlier, atrophic gastritis related to *H. pylori* infection is not considered to be involved in the development of GA-FG. On the other hand, gastric cancer associated with HGG is considered to result from chronic inflammation due to *H. pylori*

infection. Therefore, it is thought that there is no correlation between GA-FG and HGG. In our case, the GA-FG and HGG were considered to be coincidentally present in the vicinity. Furthermore, it is thought that HGG resulted from chronic inflammation due to *H. pylori* infection before eradication therapy, and pseudopyloric gland metaplasia in the fundic gland region progressed. The GA-FG may have occurred





**Figure 6** Histopathological findings of the endoscopic submucosal dissection-resected specimen. Yellow line the gastric adenocarcinoma of fundic gland type (GA-FG), Black line muscularis mucosae. The GA-FG partially invaded the submucosa layer up to 450  $\mu$ m, although it was located mainly in the deep layer of the lamina propria mucosae. Enlarged ducts of the heterotopic gastric glands were concomitantly observed just under the submucosal lesion of the GA-FG. In addition, the submucosal lesion had a poor stromal reaction.

from the remnant gastric fundic glands despite the progression of pseudopyloric gland metaplasia and spread continuous to the proximally located HGG.

Until recently, GA-FG has been recognized as cancer arising from gastric mucosa without atrophic change<sup>[2]</sup>. However, cases of GA-FG arising from gastric mucosa with atrophic change have now been reported<sup>[13]</sup>. Together with these cases, our case suggests that GA-FG could occur even from the gastric mucosa with atrophic change, where HGG could be present, provided the remnant gastric fundic glands exist. This is an important case demonstrating that when performing endoscopy, one needs to keep in mind the possibility of GA-FG presenting on the gastric mucosa with atrophic change, chronic gastritis, or intestinal metaplasia.

## COMMENTS

### Case characteristics

A 58-year-old man with epigastric pain but no other symptoms.

### Clinical diagnosis

A gastric adenocarcinoma of fundic gland type (GA-FG) was suspected based on the histological examination of the biopsy specimens obtained from the submucosal tumor-like lesion that revealed atypical cells mimicking fundic gland cells with mildly enlarged nuclei.

### Differential diagnosis

Gastric submucosal tumors, including leiomyoma, leiomyosarcoma, gastrointestinal stromal tumor, and lipoma.

### Laboratory diagnosis

Initial laboratory findings were within the normal limits.

### Imaging diagnosis

Esophagogastroduodenoscopy revealed a 10 mm submucosal tumor-like lesion in the lesser curvature of the upper third of the stomach, which had a regular microvascular pattern and a regular microsurface pattern based on narrow-band imaging with magnifying endoscopy.

### Pathological diagnosis

An endoscopic submucosal dissection (ESD)-resected specimen revealed GA-FG spreading to heterotopic gastric glands (HGG) in the submucosa because the submucosal lesion of the GA-FG had a poor stromal reaction and was located just above the HGG.

### Treatment

ESD as excisional biopsy and total gastrectomy.

### Related reports

Although there are a few case reports of regular histological type of gastric cancer spreading to HGG, this is the first case of GA-FG spreading to HGG.

### Term explanation

GA-FG, which differentiates into chief cells, is a new histological type of gastric cancer proposed by Ueyama *et al* in 2010. HGG, which are observed in the submucosa, are considered to be paraneoplastic lesions.

### Experiences and lessons

We need to keep in mind the possibility of GA-FG presenting on the gastric mucosa with atrophic change, chronic gastritis, or intestinal metaplasia.

### Peer-review

Dear Editor, this is well done case report with literature review. Authors described the case extensively and compare it against the literature. Also they provided excellent documentation and provided all necessary explanations.

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