


## CASE REPORT

# Successful resection of gastric cancer arising from a heterotopic gastric gland in the submucosa by endoscopic submucosal dissection

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## Abstract

Heterotopic gastric gland (HGG)-originating early gastric cancer was endoscopically resected. We resected the HGG, widely marked the perimeter outside the submucosal tumor-like area, injected from outside the markings into the submucosa, dissected the muscular layer, and used fine-tip hood. HGG removal and ensuring negative horizontal and vertical margins are critical.

## KEYWORDS

endoscopic submucosal dissection, endoscopic ultrasound, gastric cancer, heterotopic gastric mucosa, submucosal tumor

## 1 | INTRODUCTION

Although a heterotopic gastric gland (HGG) in the submucosa is a benign disease, some rare cases of malignancy originating from HGG have been reported previously.<sup>1–10</sup> In these reports, the tumors underwent surgical resection initially or after endoscopic resection (ER) because of margin involvement,<sup>3–7,9</sup> except in two reports where the treatment was completed by endoscopic submucosal dissection (ESD) alone.<sup>8,10</sup> We report a case of gastric cancer arising from HGG that was successfully resected using ESD. Moreover, we present tips for resecting HGG-originating cancer endoscopically, as well as high-quality images of endoscopy, endoscopic ultrasound (EUS), and histopathological findings.

## 2 | CASE HISTORY/EXAMINATION

A 62-year-old male patient with a history of *Helicobacter pylori* eradication had reflux symptoms of gastric acid, and his regular doctor prescribed a potassium-competitive acid blocker to suppress the symptoms and esophago-gastroduodenoscopy (EGD) for screening the cause of the symptoms. He had no other notable medical history, and his family had no history of malignant disease. EGD showed a gastric submucosal tumor (SMT), and forceps biopsy was performed. Histopathological assessment revealed a fundic gland-type adenocarcinoma. The patient was then referred to our center.

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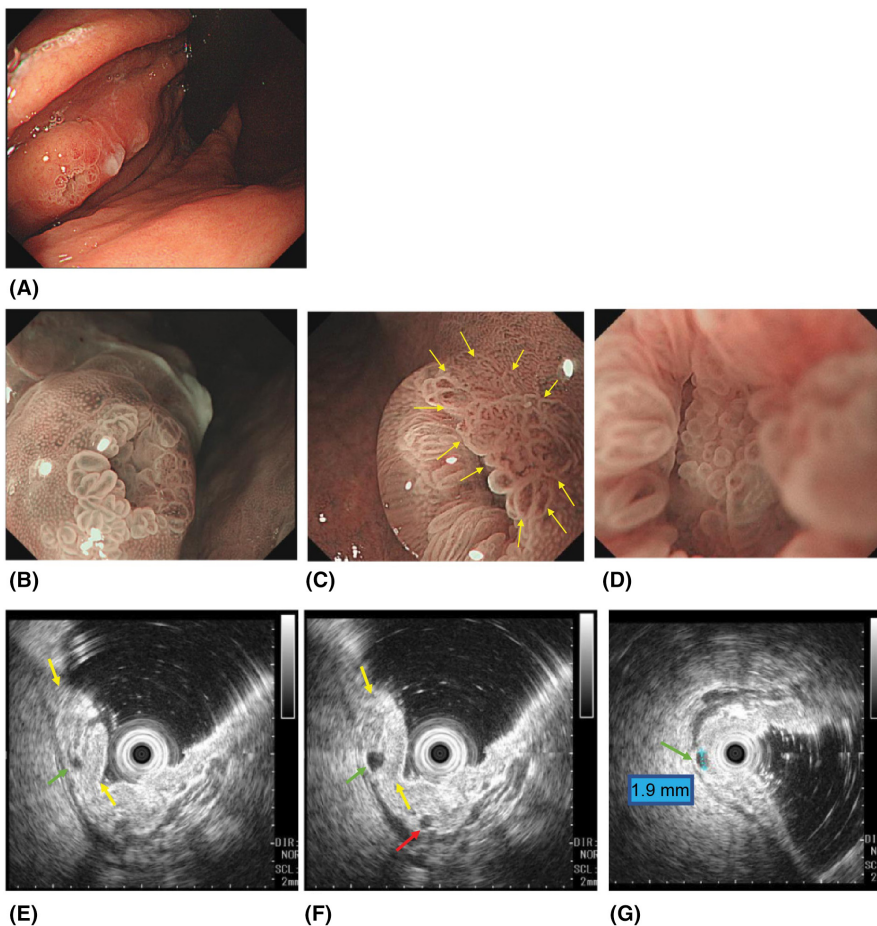
At our center, EGD was performed again. Mild atrophic gastritis of grade C-2 according to the Kimura–Takemoto atrophic-border classification was observed in the stomach.<sup>11</sup> An SMT with a diameter of 10 mm was observed at the lesser curvature of the upper body. Although the tumor was mainly covered by reddish normal mucosa, it had a central pit with clear viscous liquid that represented mucosal folding (Figure 1A). In narrow-band imaging, the mucosa around the central pit and inside the pit was composed of a villi-like structure, and focally, it had an epithelial tumor-like irregular structure with dilated microvessels (Figure 1B–D). EUS with a thin probe of 20 MHz showed a 1.9-mm submucosal cystic lesion connected to the pit without invasion to the muscularis propria (Figure 1E–G). Additionally, we observed another cyst in the submucosal layer adjacent to the lesion, which seemed to be another HGG (Figure 1F, red arrow).

### 3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

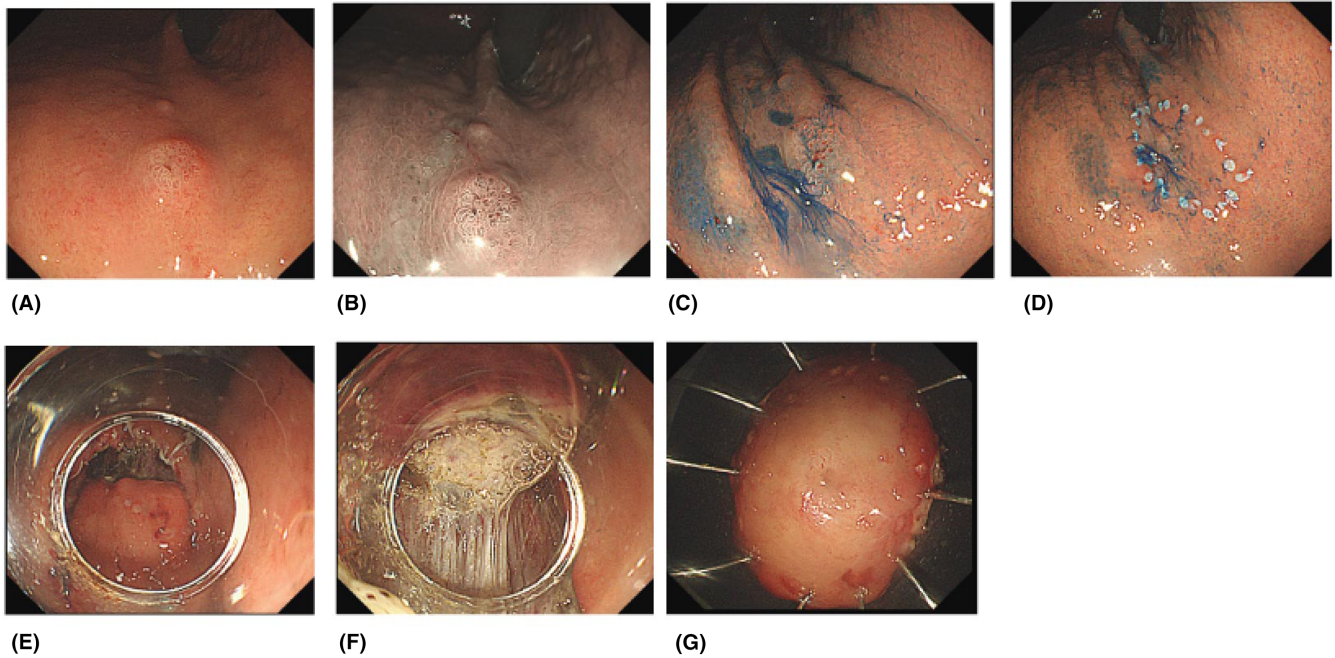
We judged that the cancer was arising from HGG and could be completely resected along with HGG by ESD,

since HGG was limited within the submucosal layer. Written informed consent was obtained from the patient for ESD.

ESD was performed 2 months after referral to our center (Figure 2A–H). The perimeter of the lesion was marked using small multiple cautery units made by the tip of DualKnife (Olympus Optical Co., Ltd., Tokyo, Japan) to clarify the range (Figure 2D). Though cystic portion under the mucosa that was connected to central pit was judged to be limited in protruded area by EUS, the markings were made 5 mm outside the SMT-like protruded area, because the HGG may have spread widely in the non-elevated area. Another submucosal cyst was noted 5 mm outside the protruded area, and we considered that the cyst may be histologically connected to the main HGG, although no definite connection was observed between the cystic portions by EUS. The high-frequency generators used were VIO300D (ERBE Elektromedizin GmbH, Tübingen, Germany). Submucosal injection was performed to lift the mucosal layer by using glycerol (10% glycerol and 5% fructose, Chugai Pharmaceutical Co., Tokyo, Japan) plus MucoUp (0.4% sodium hyaluronate; Johnson & Johnson, New Brunswick, New Jersey, USA) with a small amount of indigo carmine as the injection solution. The injection was carefully performed from outside the marked area to



**FIGURE 1** Endoscopic appearance of the tumor. (A) An SMT with a diameter of 10 mm covered by slightly reddish normal mucosa with a central pit. A clear viscous liquid flowed from the pit. (B–D) Narrow-band imaging. The mucosa around the central pit and inside the pit had a villi-like structure with a demarcation line from the peripheral normal mucosa. The yellow arrows indicate cancerous areas with irregular dilated vessels. (E–G) Endoscopic ultrasound showed a 1.9-mm cystic lesion (green arrow) inside the SMT (yellow arrow), which was connected to the central pit. Inside the anechoic area, highly echogenic lesions representing villi-like structures were observed. Another cyst was observed in the submucosal layer adjacent to the lesion (red arrow). SMT: submucosal tumor



**FIGURE 2** Endoscopic submucosal dissection of the tumor. (A) White-light appearance at the date of ESD. (B) Narrow-band imaging appearance. (C) White-light appearance after indigo carmine spray. (D) Perimeter marking was performed using DualKnife. (E) A circumferential mucosal incision after submucosal injection. (F) Deep submucosal dissection with direct vision of the HGG and muscular layer. (G) Post-ESD ulcer. HGG was removed without perforation. (H) Resected specimen was 25 mm in size. ESD, endoscopic submucosal dissection; NBI, narrow-band imaging; HGG, heterotopic gastric gland

avoid puncture of the HGG. A circumferential mucosal incision (Figure 2E) and submucosal dissection (Figure 2F) were performed using DualKnife. We paid attention to avoid damage to the deep side of the HGG by the device and dissected as deep as possible, that is, superior to the muscular layer with direct vision using an ST hood (FUJIFILM Co., Ltd., Tokyo, Japan) in a fine-tipped shape (Figure 2F). Finally, the whole HGG containing the cancerous lesion was successfully resected en bloc in 41 min without any heat damage to the HGG (Figure 2G, H). No adverse events, such as perforation or bleeding, were noted during the procedure.

The resected specimens were pathologically assessed (Figure 3). H–E stain of the section that corresponds to the depressed center showed non-neoplastic mucosa infolded to the submucosa and surrounded by muscularis mucosae, which were the typical findings of HGG (Figure 3A). The cervical part of the submucosal HGG was composed of both benign and cancerous areas without an apparent border in H–E staining, whereas the surface of HGG showed clear cancerous and non-cancerous borders (Figure 3B, C). Additionally, immunohistochemical staining with Ki-67 and p53 revealed that the proportion of p53-positive cells increased gradually from the cervical portion to the surface of HGG (Figure 3D, E). On the basis of these findings, we confirmed a cancer arising from HGG in the submucosal layer. The final histopathological diagnosis was

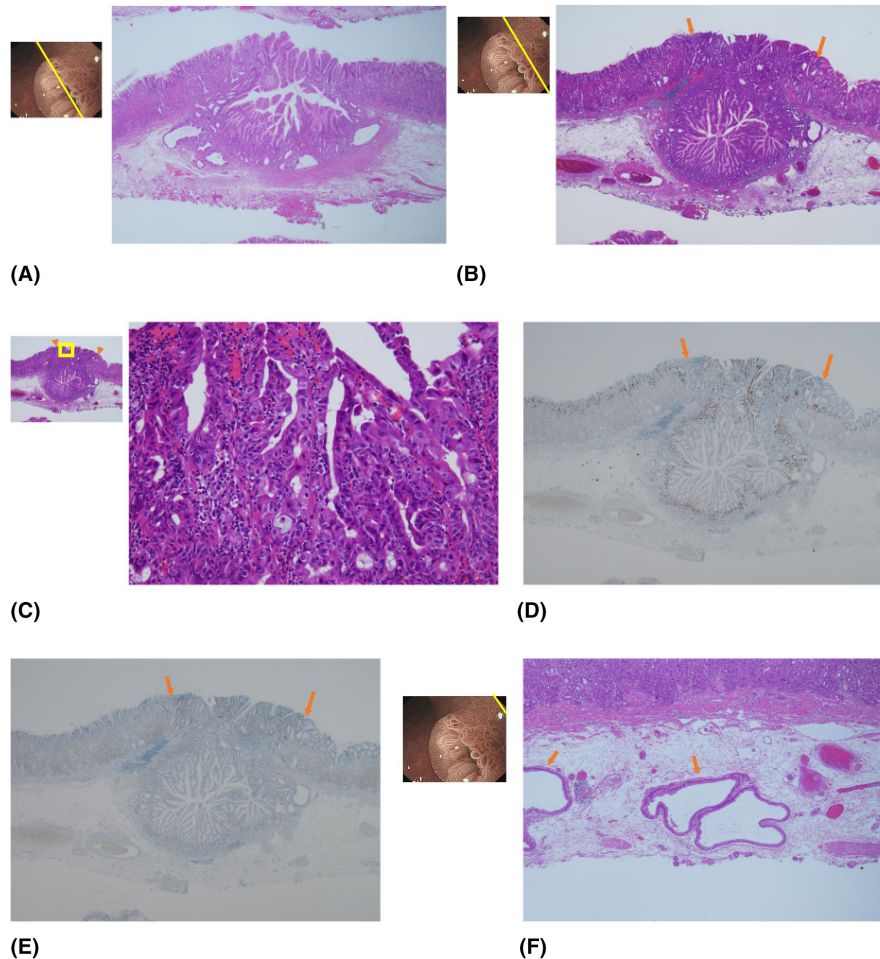
well-differentiated tubular adenocarcinoma, and definite cancerous area was 2.5 mm in diameter. Both horizontal and vertical margins and lymphovascular involvement were negative. Moreover, adjacent HGGs (Figure 1F, red arrow) were included in the resected specimen (Figure 3F).

#### 4 | OUTCOME AND FOLLOW-UP

The patient is currently undergoing a follow-up program without any additional treatment. The post-resected ulcer was completely closed, accompanied by scar formation, and EGD performed 6 months after ESD showed no local recurrence.

#### 5 | DISCUSSION

HGG in the submucosa is rare in Western countries. However, it seems to be more frequent in Japan, according to the previous reports by Rubio and Mandai, which showed that the incidence of HGG in surgically resected Japanese stomach was 20.1%.<sup>2</sup> It is believed to be an acquired disease resulting from repeated inflammatory erosion of the gastric mucosa and regeneration.<sup>12,13</sup> Endoscopically, HGG resembles a pyloric gland adenoma with downward internalization. The endoscopic difference



**FIGURE 3** Histopathological assessment. (A) H–E stain ( $\times 20$ ) of the section that corresponds to the depressed center. Non-neoplastic mucosa was infolded to the submucosa and was surrounded by muscularis mucosae. (B) H–E stain ( $\times 20$ ) of the resected specimen revealed that the whole HGG component was completely resected, and it was focally cancerous. Although the border between cancerous and non-cancerous areas was unclear, the definite cancerous area is indicated by an arrow. (C) H–E stain ( $\times 100$ ) of the cancerous lesion showing well-differentiated tubular adenocarcinoma. (D) Immunohistochemical staining for Ki-67 ( $\times 20$ ) showing that cancerous and benign areas were weakly stained. The definite cancerous area is indicated by an arrow. (E) Immunohistochemical staining for p53 protein ( $\times 20$ ) showing that cancerous and benign areas were weakly stained. The definite cancerous area is indicated by the arrow. (F) H–E stain ( $\times 40$ ) of the section showing that several adjacent HGGs other than the present lesion were also contained in the resected specimen. H–E, hematoxylin–eosin; HGG, heterotopic gastric gland

between HGG and a pyloric gland adenoma is that HGG is often characterized by multiple lesions. Histologically, the heterotopic mucosa appears as mucosal infoldings surrounded by muscularis mucosae,<sup>2</sup> demonstrating that HGG in the submucosa is an invagination of these layers and is not a neoplasm. Concordant with histological findings, non-echoic area in the submucosa connected to the central pit at the surface which represents cavity of invagination, surrounded by hypo-echoic area which represents infolded mucosa, and multiple lesions are the characteristics of EUS images of HGG.

Only few reports have described gastric carcinoma originating from HGG.<sup>1–10</sup> Imamura et al. reported that early gastric cancer arising from HGG was predominant in males, and the cancer frequently occurred in the middle third of the

stomach, based on a review of the literature.<sup>5</sup> With respect to histological findings, well-differentiated tumors were more common. If gastric cancer arising from HGG is limited to the mucosa or submucosa, it can be removed by ER.<sup>14</sup>

En bloc resection without margin involvement is essential for curability of early gastric cancer by ER. Since the cancerous areas in the HGG cannot be distinguished clearly from the non-cancerous areas in pre-treatment endoscopic examinations, all HGG lesions must be resected without heat or mechanical damage by endoscopic instruments. For this purpose, ESD is ideal among the various endoscopic procedures since it enables dissection of the deep submucosal layer with direct vision of the deeper side of the HGG lesion. Using conventional EMR, which is a much simpler procedure

than ESD, it is difficult to ensure a negative margin, especially the vertical margin.<sup>3</sup>

Some tips to resect HGG-originated cancer by ESD are as follows: (1) the cancer should be resected along with the whole HGG component, since cancerous and non-cancerous areas under the mucosa are indistinguishable; (2) perimeter marking should be made widely outside the protruded area in imaging since HGG may have extended under the non-elevated mucosa; (3) submucosal injection must be performed from outside the marked area to prevent puncturing the HGG spreading in the submucosa; (4) dissection must be performed as deep as possible to prevent heat and mechanical damage to HGG; and (5) a fine-tip hood is useful to ensure direct vision of the deeper side of the lesion. Additionally, counter-traction devices<sup>15-18</sup> may be useful. After removal of the lesion, determination of the depth of invasion and lymphovascular involvement and margin involvement by histopathological assessment is indispensable, and additional surgery should be considered according to guidelines.<sup>14</sup> Removal of the whole HGG and ensuring negative horizontal and vertical margins is critical to increase the chance of curative resection with ESD alone and avoid needless surgery.

#### AUTHOR CONTRIBUTION

Yasuhiro Inokuchi contributed to the conception and design of the study; performed treatment, preparation of study, data collection and analysis, and assessment and comparison of pathological findings and endoscopic findings; wrote the first draft of the manuscript; commented on the first draft; further revised the draft; read and approved the final manuscript. Kota Washimi contributed to the conception and design of the study, performed assessment and comparison of pathological findings and endoscopic findings, commented on the first draft, read and approved the final manuscript. Mamoru Watanabe, Kei Hayashi, Yoshihiro Kaneta, Mitsuhiro Furuta, Nozomu Machida, and Shin Maeda contributed to the conception and design of the study, commented on the first draft, read and approved the final manuscript.

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#### CONFLICT OF INTEREST

None.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ETHICAL APPROVAL

This case study did not require ethical approval from our institution's institutional review board.

#### CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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