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Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no financial conflicts of interest.

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A Rare Case of Signet Ring Cell Carcinoma Arising on Duodenal Brunner's Gland Hyperplasia Successfully Treated Via Endoscopic Resection

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Signet-ring cell carcinoma (SRCC) is a rare tumor that most commonly occurs in the stomach. Duodenal SRCCs are extremely uncommon and account for approximately 1% of duodenal adenocarcinomas. Although Brunner's gland hyperplasia (BGH) is a benign duodenal condition, studies have reported several cases of adenocarcinoma originating in an area of BGH. We report a rare case of early-stage SRCC originating in an area of BGH that was successfully treated using endoscopic mucosal resection. Based on the mucin phenotype observed in this case, it is reasonable to conclude that SRCC originated from gastric metaplasia in the area of BGH. Although BGH is a benign condition, careful evaluation is warranted for early detection of combined neoplasms.

Keywords Duodenum; Brunner's gland; Carcinoma, Signet ring cell; Endoscopic mucosal resection.

INTRODUCTION

Signet ring cell carcinoma (SRCC) is a rare tumor more commonly detected in the stomach than other sites in the gastrointestinal tract,¹ and SRCC within the duodenum is even rarer, accounting for approximately 1% of duodenal adenocarcinomas.² While Brunner's gland hyperplasia (BGH) is a benign condition of duodenum,³ which is occasionally discovered

during screening esophagogastroduodenoscopy (EGD), several cases of adenocarcinoma arising from BGH have been reported.⁴ Here, we report an extremely rare case of early-stage SRCC arising on BGH in the second portion of the duodenum, which was successfully removed by endoscopic mucosal resection (EMR).

CASE REPORT

A 74-year-old woman was referred to our gastroenterology clinic for further evaluation of a duodenal subepithelial lesion detected on a screening EGD. Local biopsy specimen showed focal atypical cell aggregation with signet ring cell features, which could not exclude SRCC. In our clinic, EGD revealed a

13 mm-sized subepithelial lesion, located in the second portion of the duodenum, and a linear erosion with locally reddish irregular mucosa was seen on the surface (Fig. 1A-D). Endoscopic ultrasonography showed a heterogeneous echogenic mass with small anechoic areas mainly located in the submucosa in favor of typical features of BGH (Fig. 1E).⁵ And the suspected SRCC seemed to be confined to the mucosal layer (inside the yellow arrow) (Fig. 1F).⁵ And the suspected SRCC seemed to be confined to the mucosal layer

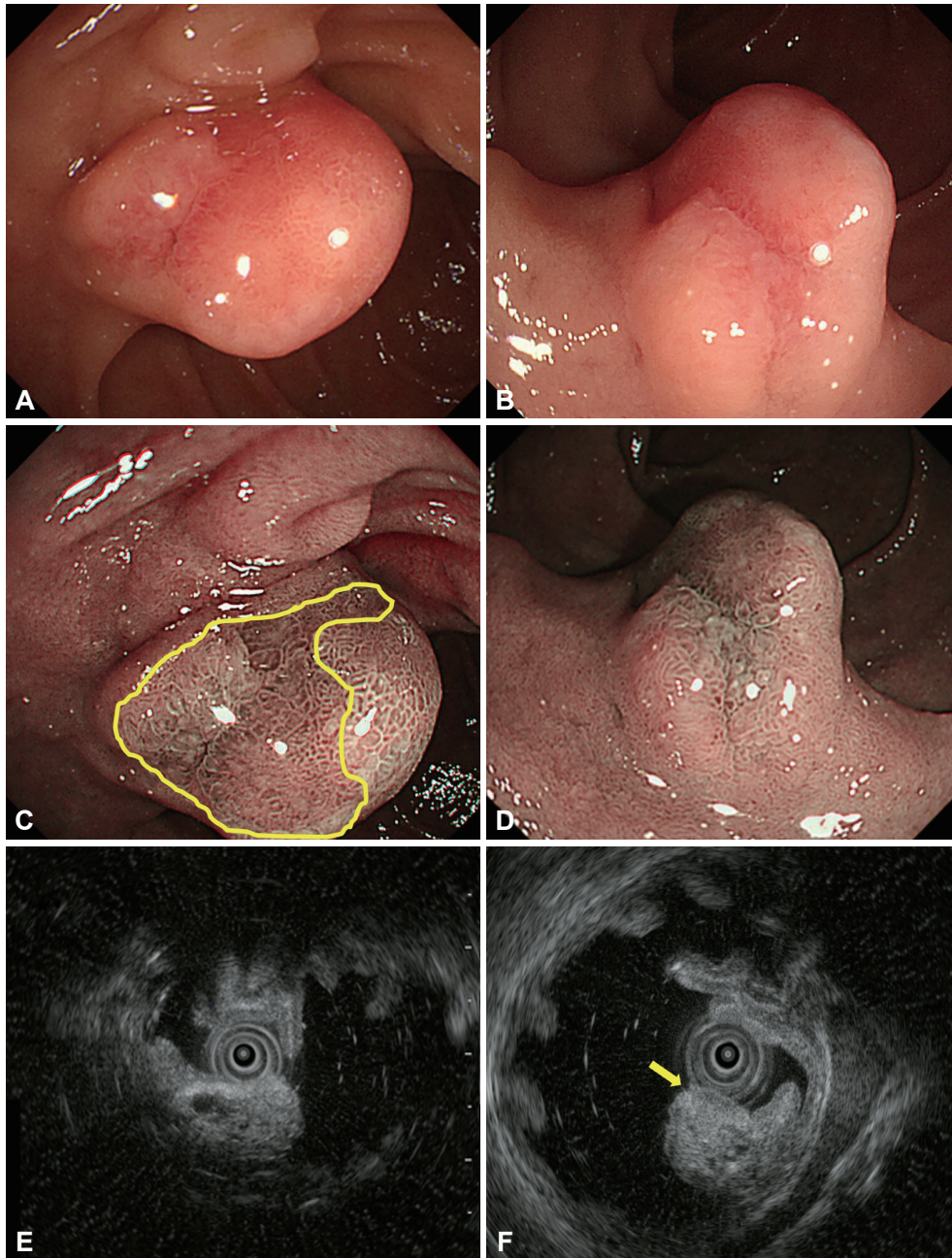


Fig. 1. Endoscopic and endosonographic findings. A and B: EGD showed a 13 mm-sized subepithelial lesion, located in the second portion of the duodenum, showing a linear erosion with locally reddish irregular mucosa on the surface. C and D: Narrow-band imaging showed abnormally distorted mucosal pattern on the surface (inside the yellow line). E: EUS revealed a mass with heterogeneous echogenicity with small anechoic areas mainly located in the submucosa in favor of typical features of BGH. F: SRCC seemed to be confined to mucosa layer (inside the yellow arrow). EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasonography; BGH, Brunner's gland hyperplasia; SRCC, signet ring cell carcinoma.

(Fig. 1F). She had no gastrointestinal symptoms, and physical examination and laboratory tests were normal. No organ or lymph node metastasis were identified by abdominal computed tomography (CT). Comprehensively, the SRCC appeared to be a minute early stage lesion confined to mucosa arising on the surface of BGH. Therefore, we planned to perform EMR rather than pancreatoduodenectomy for the lesion. After submucosal injection to lift the lesion (Fig. 2A), we totally resected the tumor using an endoscopic snare (Fig. 2B and C). And then, the resected area was closed by endoclips (Fig. 2D). Gross appearance of the resected specimen showed a 13 mm-sized subepithelial tumor, with reddish irregular mucosal surface showing abnormal vasculature via near-focus imaging (Fig. 2E and F). Pathological analysis of the resected specimen was performed. On microscopic findings, atypical cells were identified in the lamina propria in background of gastric metaplasia overlying on BGH (Fig. 3). These cells were isolated or poorly cohesive with signet ring cell features with no well-formed glands (Fig. 4A), and strongly positive for pan-Cytokeratin (AE1/AE3, epithelium specific antibodies⁶) (Fig. 4B), which is consistent with SRCC. Tumor size was 4 mm with clear lateral and vertical resection margins, and lymphovascular invasion was not seen in the specimen. On immunohisto-

chemical (IHC) findings, the tumor cells were strongly positive for MUC5AC (a marker for gastric foveolar epithelium) (Fig. 4C), and also weakly positive for MUC6 (a marker for gastric mucous neck cells or antral glands) (Fig. 4D). However, immunostainings for MUC2 (a marker for intestinal goblet cells) (Fig. 4E) and CD10 (a marker for the brush border of intestinal epithelium⁷) were negative (Fig. 4F). Finally, we diag-

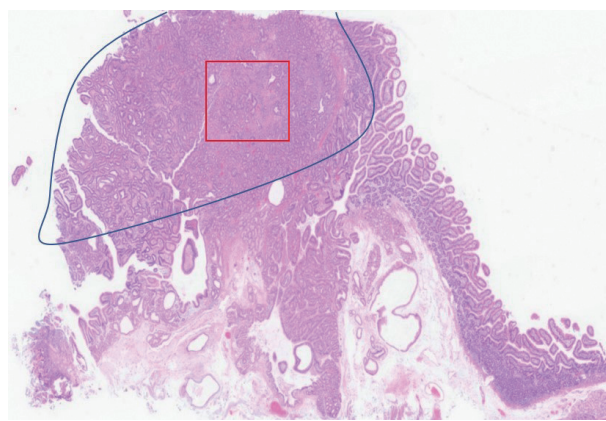


Fig. 3. Gastric foveolar metaplasia overlying BGH (blue line) is identified. Signet ring cell carcinoma (red square) is found in the center (H&E; magnification, $\times 1.25$). BGH, Brunner's gland hyperplasia; H&E, hematoxylin and eosin.

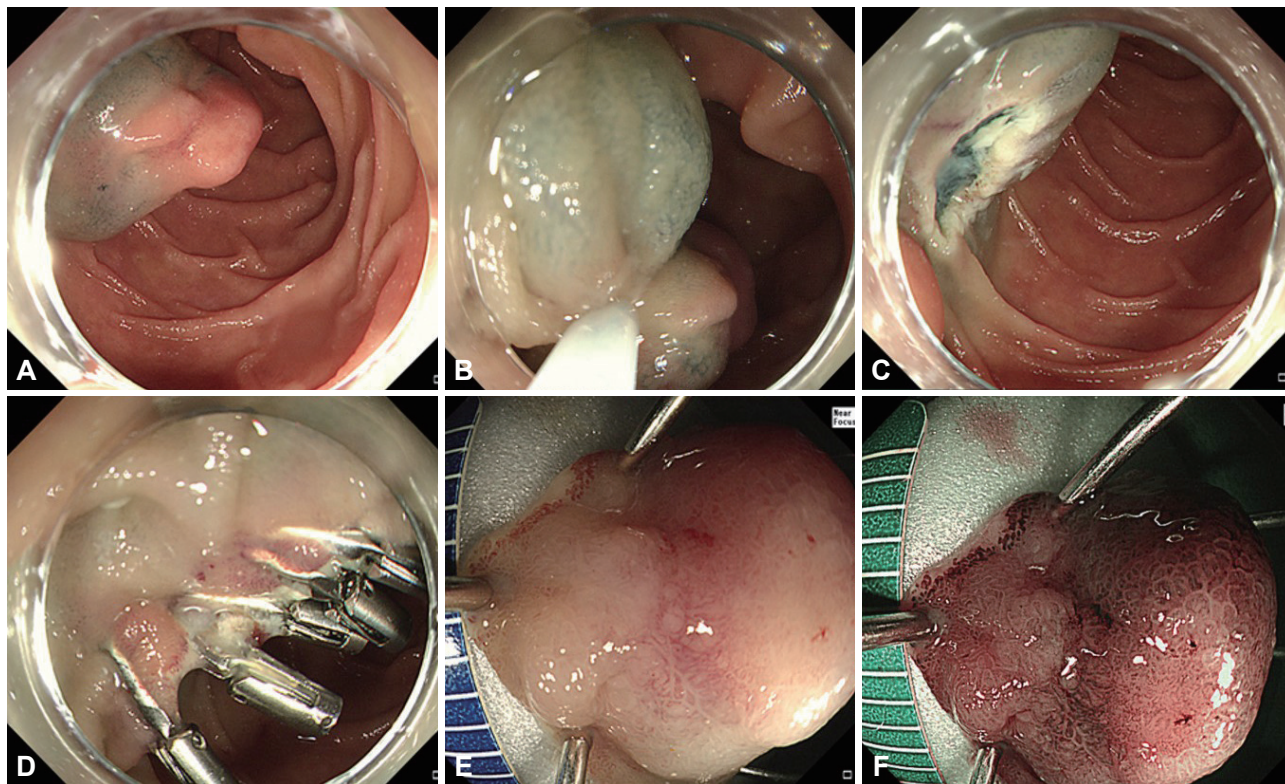


Fig. 2. Endoscopic mucosal resection. A: Submucosal injection was done to lift the lesion. B and C: The tumor was totally resected using an endoscopic snare. D: Endoclips were placed to close the defect after EMR. E and F: Gross appearance of the resected specimen showed a 13 mm-sized subepithelial tumor, with a reddish irregular mucosal surface showing abnormal vasculature via near-focus imaging. EMR, endoscopic mucosal resection.

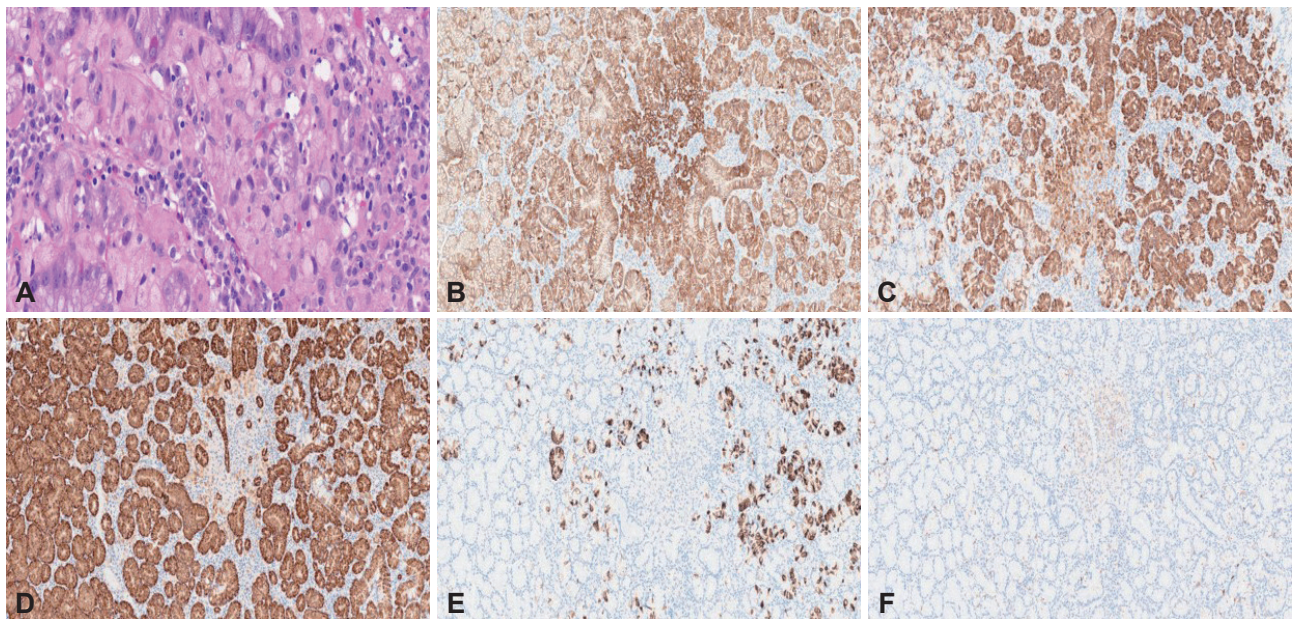


Fig. 4. Histopathological findings. A: Tumor cells show signet ring cell features, which are characterized by abundant intracytoplasmic mucin with an eccentrically placed nucleus (H&E; magnification, $\times 400$). On immunohistochemical findings, tumor cells were positive for panCK (B), MUC5AC (C) and weakly positive for MUC6 (D), but negative for MUC2 (E) and CD10 (F) (magnification, $\times 100$). H&E, hematoxylin and eosin; panCK, pan Cytokeratin; MUC5AC, mucin 5AC; MUC6, mucin 6; MUC2, mucin 2.

nosed SRCC probably originated from gastric foveolar metaplastic epithelium arising on BGH. The patient was discharged with no procedure-related complications. Now we plan 6-month follow-up with EGD and abdominal CT in the first year, and regular annual follow-ups from years 2 to 5.

DISCUSSION

We recently encountered a very rare case of SRCC arising on BGH in the second portion of the duodenum. During a screening EGD, the endoscopist did not miss the minute surface abnormality on BGH, and could detect an early-stage SRCC.

SRCC is mainly found in the stomach, and is a very rare occasion in the duodenum. Particularly, non-ampullary SRCC is extremely uncommon, and only a few cases have been reported until recently.⁸ Moreover, BGH is generally considered a benign condition, commonly existing in the first and the second portion of the duodenum.⁴ Brunner's glands are mucus-secreting gland located in the deep mucosa or submucosa of the duodenum,³ and BGH defined as a benign proliferation of mature Brunner's glands is usually presented as a subepithelial lesion on EGD.^{9,10} On endoscopic ultrasonography, BGH commonly appears a round, well-circumscribed mass mainly located in the submucosal layer, and shows variable echogenicity (hyperechoic, isoechoic, hypoechoic or mixed) demonstrating solid or cystic structures.³ Although duodenal BGHs are mostly benign, several cases of adenocarcinomas arising on

BGH have been reported. Therefore, careful endoscopic inspection is important not to overlook the possibility of combined dysplasia or carcinoma.

Previous studies hypothesized that duodenal SRCC might be originated from heterotopic gastric-type mucosa or de novo from duodenal mucosa,⁸ and according to morphotype and/or mucin immunophenotype confirming cellular origin, duodenal adenocarcinomas are classified into two groups: gastric-type or intestinal type.¹⁰ Gastric-type adenocarcinoma express MUC5AC and MUC6, known as gastric phenotype markers, whereas intestinal-type adenocarcinoma generally express MUC2, CD10, and CDX2. Some researchers presented a few cases of primary non-ampullary SRCC with mixed gastric foveolar and intestinal phenotypes, while Lee et al.⁸ reported a case of primary non-ampullary duodenal SRCC only with intestinal type, in which no ectopic gastric tissue or gastric-type metaplasia were found around the tumor, and IHC profiles (positive for MUC2 and negative for MUC5AC and MUC6) suggested that the tumor cells were derived from duodenal goblet cells. In the present case, tumor cells arising on BGH were positive for MUC5AC and MUC6, but negative for MUC2 and CD10, which were indicative of gastric phenotype duodenal SRCC. Previous studies suggested that gastric foveolar metaplasia could arise from generative cell zones formed in the Brunner's gland, following duodenal ulcer and mucosal regeneration after inflammation.¹⁰

Duodenal adenocarcinomas are most frequently treated by

surgical resection including pancreatoduodenectomy (36.0%), partial duodenectomy with gastrectomy (28.0%), or partial duodenectomy (16.0%), while endoscopic treatment have been reported in 12.0%.¹¹ In our case, early detection of the SRCC made it possible to perform curative endoscopic resection.

In conclusion, we reported an extremely rare case of early-stage SRCC probably originated from gastric foveolar metaplastic epithelium arising on BGH in the duodenum. Although BGH is a well-known benign condition, endoscopists have to be aware that BGH could be combined with neoplastic change. Careful endoscopic inspection is important whether the color change or mucosal irregularities are identified on the surface of BGH, and biopsy confirmation is required if necessary. Early detection is vital to make a curative EMR for this lesion.

Authors' Contribution

Conceptualization: Bong Eun Lee, Kyung Bin Kim. Data curation: Hae Rin Lee. Formal analysis: Bong Eun Lee. Investigation: Hae Rin Lee, Bong Eun Lee. Methodology: Kyung Bin Kim. Project administration: Hae Rin Lee. Resources: Moon Won Lee, Dong Chan Joo. Software: Moon Won Lee, Dong Chan Joo. Supervision: Gwang Ha Kim. Validation: Moon Won Lee. Visualization: Dong Chan Joo. Writing—original draft: Hae Rin Lee. Writing—review & editing: Bong Eun Lee, Kyung Bin Kim. Approval of final manuscript: all authors.

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Ethics Statement

This study received exemption from consent and review from the Pusan National University Hospital Research Ethics Review Committee (IRB No. 2401-001-134).

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