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Case Series

Three Types of Subepithelial Lesion-Like Gastric Cancer Including a New Entity of Gastric Adenocarcinoma

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Keywords
Gastric cancer · Gastric adenocarcinoma · Subepithelial lesion · Submucosal tumor · Gastric adenocarcinoma of fundic gland type

Abstract
Gastric subepithelial lesions (SEL) are usually found incidentally during esophagogastroduodenoscopy. Most gastric SELs are benign lesions, such as leiomyoma and pancreatic rests. However, neoplastic lesions including neuroendocrine tumors, gastrointestinal stromal tumors, and certain types of gastric adenocarcinoma (GA), such as the recently WHO-classified fundic gland type adenocarcinoma, may be found. The lack of simple and established diagnostic methods for SEL remains a clinical challenge. Standard biopsy is suboptimal for diagnosis due to the subepithelial location of lesions and is therefore often omitted. Furthermore, guideline-based algorithmic approaches for diagnosing SEL also differ between Japan and the USA. In this case series, we describe three cases of gastric SEL that were subsequently diagnosed as GA. Case 1 was a fundic gland type (chief cell predominant type) adenocarcinoma; Case 2 was a poorly differentiated GA; Case 3 was an advanced GA, found after 4 serial years of endoscopic follow-up for SEL. While standard biopsy led to successful diagnosis in the first 2 cases, no standard biopsy was performed during surveillance in Case 3, making its diagnostic effectiveness unclear. The third case highlights the importance of longitudinal observation for endoscopic mucosal alterations that may suggest certain types of GA. Clinicians should be aware that standard biopsy may play an important role in the evaluation of malignant gastric SEL-like lesions. It is crucial to remain vigilant for surface changes in SEL and not to summarily omit standard biopsy.

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Introduction

Gastric subepithelial lesions (SEL) are usually incidental findings of esophagogastroduodenoscopy (EGD) [1] and are not uncommon. Its prevalence is 0.36% in routine EGD [2]. Gastric SEL includes both benign and potentially malignant lesions. Benign lesions include leiomyomas, pancreatic rests, and duplication cysts, while malignant lesions include stromal tumors, neuroendocrine neoplasms, lymphoma, metastatic tumors, glomus tumors, and gastric adenocarcinoma (GA). The prevalence of GA exhibiting SEL features has been reported to range from 0.2% to 0.62% [3] and several cases were reported [3–6].

As there is no established diagnostic method for SEL lesions, they may be initially misdiagnosed as benign, delaying care for serious disease. As such, SEL-like GA remains a potential pitfall in EGD of which physicians should remain aware.

Typically, poorly differentiated adenocarcinoma, fundic gland-type GA (chief cell predominant type) (GA-FG-CCP), and neuroendocrine tumors have been reported to have an SEL-like appearance [7–9]. Here, we reported 3 cases of GA with SEL-like appearance and discussed the usefulness of standard biopsy for gastric SEL.

Case Report/Case Presentation

Case 1

A 75-year-old woman with a history of type 2 diabetes and hyperlipidemia underwent screening EGD as part of a comprehensive preventive health check-up in 2012. EGD revealed a 10 mm protuberance with dilated vessels with branching architecture on overlying mucosa on the greater curvature of upper gastric body (shown in Fig. 1a). She was diagnosed with SEL and was closely surveilled by EGD, receiving standard biopsy in 2014, 2015, 2017, and 2018. Histopathology of standard biopsy in 2014, 2015, and 2017 were negative for cancer; subsequent samples taken in 2018 suggested adenoma [10]. There were no remarkable changes in EGD findings in this period (shown in Fig. 1b). *Helicobacter pylori* (*H. pylori*) infection was excluded by histology. Endoscopic ultrasound (EUS) showed a 10 mm-diameter hypoechoic area, involving the second layer of the gastric wall, without disruption of the third

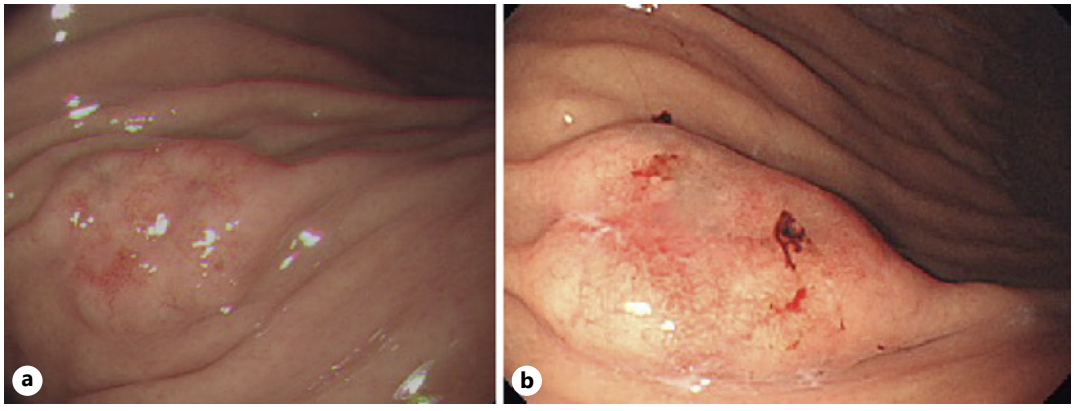

Fig. 1. Endoscopic findings of Case 1. **a** A 10 mm protuberance with bridging folds and dilated surface vessels on its surface was noted on the greater curvature of gastric upper body in 2012. Atrophic gastritis was noted in antrum. **b** No remarkable change is seen on EGD regarding protuberance on upper body in 2018. Standard biopsy suggested tubular adenoma although four standard biopsies from same lesion in 2012, 2014, 2015, and 2017 did not show any neoplastic findings.

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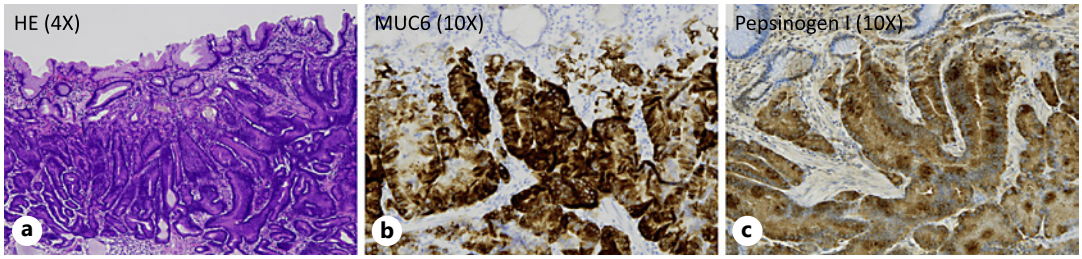

Fig. 2. Histopathological findings of Case 1. **a** Gastric adenocarcinoma of fundic-gland type. Atypical epithelium resembling fundic glands is present, note the preserved surface foveolar epithelium. **b** Immunohistochemistry for MUC6, the tumor cells showing diffuse expression. **c** Immunohistochemistry for pepsinogen-I, the tumor cells showing diffuse expression.

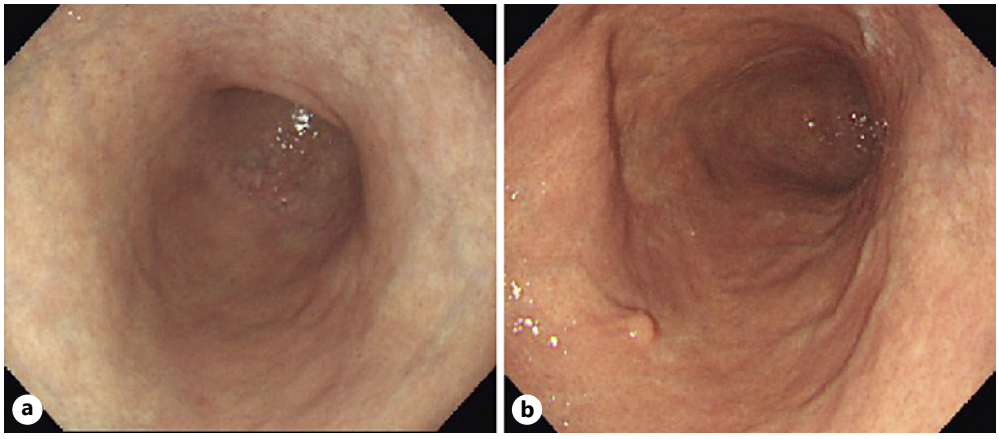

Fig. 3. Endoscopic findings of Case 2. **a** EGD in 2018 showed only atrophic gastritis in antrum and lesser curvature of body without any local lesions. **b** A 6 mm protuberance with whitish mucosa was noted on the greater curvature of gastric lower body in 2019.

layer. Endoscopic submucosal dissection (ESD) was performed with a subsequent diagnosis of early GA (T1aN0M0); histopathological findings suggested GA-FG-CCP with submucosal invasion (shown in Fig. 2a). Immunohistochemistry was positive for both MUC 6 and pepsinogen-I (shown in Fig. 2b, c) [9]. Since both MUC 6 and pepsinogen-I are chief cell markers, these results were compatible with GA-FG-CCP [11].

Case 2

A healthy 56-year-old woman had undergone annual screening EGDs since *H. pylori* eradication at 43 years of age. Although EGD in 2018 showed only atrophic gastritis (shown in Fig. 3a), a 6 mm protuberance with bridging fold was found on the greater curvature of the gastric lower body in 2019 (shown in Fig. 3b). The mucosa surrounding this lesion was pale. Histopathological examination of a tissue sample from standard biopsy identified poorly differentiated adenocarcinoma, including signet-ring cell carcinoma without involvement of surface epithelium. After EUS-confirmation of absence of tumor invasion into the third layer of the stomach, as well as the absence of any metastatic lymph nodes on abdominal CT, the lesion was diagnosed with T1aN0MO and was resected via ESD. Histopathological findings showed a poorly cohesive signet-ring cell phenotype [9] with submucosal and lymphatic invasion (shown in Fig. 4). No vessel invasion was observed. Horizontal margins were negative, but vertical margin was positive for cancer, prompting additional surgical resection.

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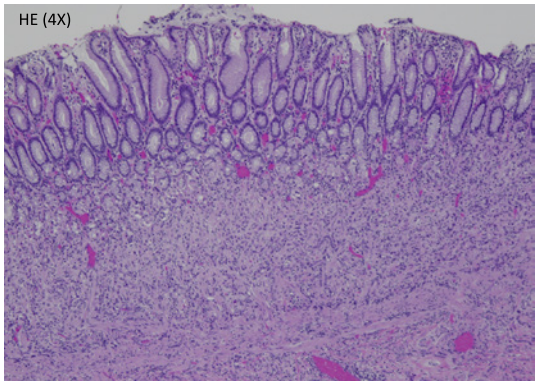

Fig. 4. Histopathological findings of Case 2. Poorly differentiated adenocarcinoma cells are present in the glandular neck without involvement of surface epithelium.

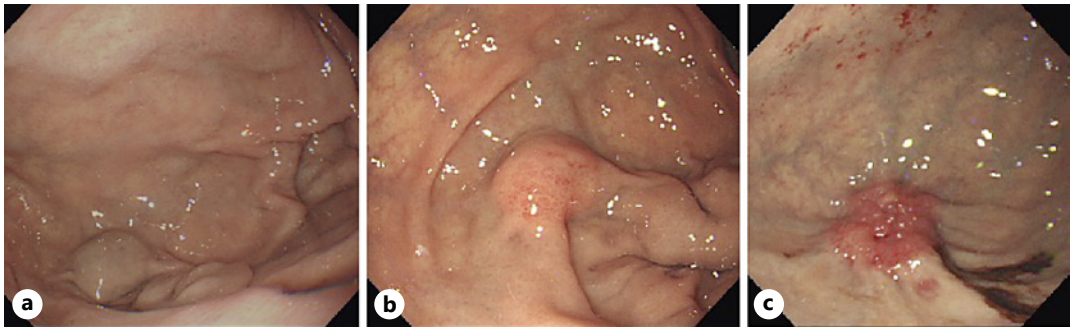

Fig. 5. Endoscopic findings of Case 3. **a** A 10 mm protuberance with bridging folds was noted on the greater curvature of gastric fundus in 2015. Atrophic gastritis was noted in antrum and lesser curvature of body. **b** Vessel dilatation appeared on the surface of protuberance in 2018. **c** A remarkable change was noted on the protuberance in gastric fundus. Depressive lesion covered by irregular reddish mucosa was noted at the same site of protuberance in 2018.

Case 3

A 75-year-old hypertensive man with a history of *H. pylori* eradication in 2001 was diagnosed with a 10 mm protuberance in the gastric fundus with bridging fold and normal overlying mucosa on EGD in 2015 (shown in Fig. 5a). He was followed-up annually with EGD for another 4 years. Mucosal change with vessel dilatation was noted on EGD in 2018 (shown in Fig. 5b), but no biopsy was performed at that time as the size, less than 2 cm, had not changed and the patient had remained asymptomatic, suggesting that it was unlikely to be malignant. In 2019, he was unexpectedly diagnosed with advanced gastric cancer with remarkable changes seen in the irregular reddish mucosa on endoscopy (shown in Fig. 5c). Histopathology of standard biopsy specimens confirmed adenocarcinoma. The tumor's clinical stage was T2N0M0. Histopathological examination after laparoscopic fundoplication identified moderately differentiated tubular adenocarcinoma with serosal, lymphatic, and vessel invasion (shown in Fig. 6a, b) [9].

Discussion/Conclusion

We experienced three types of SEL-like GA including GA-FG-CCP, poorly differentiated GA, and moderately differentiated adenocarcinoma. Case 1 and Case 2 were diagnosed as gastric adenoma and GA, respectively, using standard biopsy during EGD. In Case 3, standard biopsy

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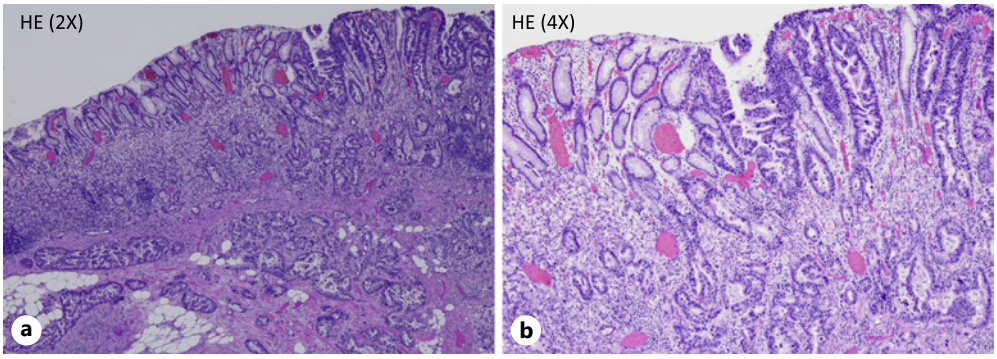

Fig. 6. Histopathological findings of Case 3. **a** Adenocarcinoma cells are mainly present in the submucosal area with partial surface invasion. **b** Moderately differentiated tubular adenocarcinoma. Irregular shaped atypical glands are present.

was not performed until remarkable changes were seen on follow-up EGD. These three cases included GA-FG-CCP, poorly differentiated GA, and moderately differentiated adenocarcinoma.

Case 1 was a GA-FG-CCP, a lesion first described in 2010 [7] and recently classified as a new entity per WHO [9]. GA-FG-CCP represents 1.6% of all GA and 60% of which have been reported to have a SEL-like appearance, typically with dilated mucosal vessels with branching architecture [8]. As the frequency of *H. pylori*-related gastric cancers decreases [12, 13], the proportion of GA-FG-CCP has been reported to be increasing. While the appearance of the lesion was not typical for malignant neoplasms, standard biopsy suggested malignancy. This GA-FG-CCP was a low-grade malignancy, corroborating the findings of a previous case report [13].

Case 2 was a poorly differentiated GA mimicking SEL. An atypical mucosal pallor overlying the lesion prompted a standard biopsy, by which the diagnosis of GA was easily made. Although 2 cases of poorly differentiated GA mimicking SEL with central depression were reported [3, 14], our case was the first report of SEL-like poorly differentiated GA with superficial mucosal pallor.

Case 3 was a moderately differentiated tubular adenocarcinoma. Despite close EGD follow-up for 4 years after initial identification of the gastric fundus protuberance, biopsy was not performed during the follow-up period, in spite of a diffuse mucosal erythema seen on EGD 1 year prior to diagnosis of GA. Case 2 and Case 3 were so-called post-*H. pylori* eradication GA, but Case 1 was not associated with *H. pylori* infection.

Standard biopsy is not usually effective for tissue diagnosis of SEL and alternative methods such as jumbo biopsy and unroofing techniques, and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) are recommended based on individual case characteristics. Management algorithms combining various diagnostic methods have been reported in the American Society of Gastrointestinal Endoscopy (ASGE) guidelines [15].

Per GIST management guidelines in Japan, as the first step, standard biopsy is recommended to initially rule out an epithelial lesion [16]. However, in actual practice, standard biopsy is not routinely performed due to low diagnostic yield and the risk of bleeding [17]. Diagnostic strategies for this guideline largely depend on the size of SEL at index EGD. For example, SELs less than 2 cm are recommended to be followed-up without additional diagnostic procedures. This management algorithm differs from ASGE guidelines [15], which recommend EUS for SELs of any size to clarify their location (2nd, 3rd, or 4th layer) at the first step. ASGE guidelines recommend additional invasive procedures such as EUS-FNA after excluding vascular lesion, cystic lesion, and lipoma, regardless of SEL size. Standard biopsy is not described at any step in the diagnosis of SELs per ASGE guidelines.

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Although EUS should be performed on SELs, it is practically difficult to perform EUS for all such lesions due to limited resources. Thus, we think that at least one standard biopsy is an affordable and prudent diagnostic strategy considering the possibility of rare types of GAs and gastric neuroendocrine tumors, which originate from the mucosal layer and invade into the submucosa [18].

In conclusion, the diagnosis of gastric SEL continues to be rife with potential pitfalls. It is therefore critical to carefully identify common endoscopic features of GA-FG-CCP and poorly differentiated adenocarcinoma. The most common features of GA-FG-CCP include SEL shape, whitish color, dilated vessels with branching architecture, and a background mucosa lacking atrophic changes [7]. Common features of poorly differentiated adenocarcinoma include a mucosal pollor or central depression. It cannot be overemphasized that clinicians should be vigilant for surface change of SELs and that even standard biopsy may play a role in some categories of SEL, especially in gastric cancers and neuroendocrine tumors.

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Statement of Ethics

All 3 patients have given their written informed consent to publish their case (including publication of images). Information revealing the subject's identity is to be avoided. All patients should be identified by numbers or aliases and not by their real names. This study protocol was reviewed and approved by the internal review board at St. Luke's International University, approval number [20R-136].

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Fumio Omata, Takashi Ikeya, and Kazuki Yamamoto designed the study. Naoki Kanomata made histopathological diagnosis including immunohistochemistry. Kazuki Yamamoto wrote the manuscript. Fumio Omata, Gautam Anil Deshpande, and Naoki Kanomata edited the

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manuscript. Koichi Takagi critically reviewed the manuscript. All the authors contributed to discussions and approved the final manuscript.

Data Availability Statement

All data that support the findings of this study are included in this article.

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