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Submucosal Tumor-like-shaped Low-grade Well-differentiated Adenocarcinoma with Gastric Phenotype Arising in the *Helicobacter pylori*-negative Stomach at Medical Check-up: A Report of Three Cases

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Abstract

We describe three cases of submucosal tumor (SMT)-like-shaped low-grade well-differentiated adenocarcinoma with gastric phenotype (LG-WDA-G) arising in the *Helicobacter pylori*-negative stomach that were revealed during esophagogastroduodenoscopy (EGD) screening. In Case 1, a whitish 7-mm-diameter SMT-like lesion in the fornix of a 42-year-old man was revealed. Dilated-branched vessels and pigmentation were also observed on the surface of the lesion. Biopsy specimens displayed a mild structural variant but no evidence of malignancy. Endoscopic submucosal dissection was performed as a diagnostic treatment. In Case 2, EGD revealed a gentle protrusion 7-mm in size in the fornix of a 49-year-old man. Dilated-branched vessels and prolongation of the intervening part between the crypts were observed at the surface of the lesion. Biopsy revealed adenocarcinoma. Histologically, in both cases, each tumor was located in the deep mucosal layer covered with the non-neoplastic foveolar epithelium formed by irregularly shaped glands composed of slightly atypical glandular cells resembling fundic glands cells. Immunostaining results revealed MUC6 and pepsinogen-I expression. These results confirmed the diagnosis of LG-WDA-G; specifically, gastric adenocarcinoma of the fundic gland type. In Case 3, a 10-mm SMT-like elevated lesion with central erosion was observed on the greater curvature of the middle gastric body in a 66-year-old man. Biopsy specimens showed atypical glands but indefinite for neoplasia. Endoscopic ultrasonography findings showed an isoechoic tumor with several cystic legions in the submucosal layer. According to immunohistochemistry, LG-WDA-G with MUC6, pepsinogen-I, and MUC5AC-positive tumor cells were invading the submucosal layer significantly along heterotopic gastric glands. Additional surgery revealed no lymph node metastasis.

Keywords low-grade well-differentiated adenocarcinoma with gastric phenotype, gastric adenocarcinoma of fundic gland type, submucosal heterotopic gastric glands, submucosal-tumor-like-shaped tumor

Although *Helicobacter pylori* (*H. pylori*)-negative gastric cancers are rare, it is expected that the frequency of *H. pylori*-negative gastric cancers will increase because the incidence of *H. pylori* infection is declining due to either improvement in water supply and sewerage systems or the increasing number of eradications in Japan. This report describes three cases of *H. pylori*-negative gastric cancers with a submucosal tumor (SMT)-like appearance, diagnosed as low-grade well-differentiated adenocarcinoma with gastric phenotype (LG-WDA-G) at medical check-up.

Case Report (Three Cases)

Case 1

A 42-year-old man, who had no history of eradication therapy, underwent screening for esophagogastroduodenoscopy (EGD). The background mucosa revealed no endoscopic findings of atrophic gastritis, while serum test results were negative for staining with *H. pylori* antibody. The examination revealed a flat

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elevated, 7-mm-diameter, smooth, whitish, SMT-like lesion in the fornix (**Fig. 1a**). Proliferation of dilated vessels and pigmentation were also observed at the surface of the lesion using a conventional endoscopy. A biopsy was performed. The tumor was soft when grasped with forceps (**Fig. 1b**). Biopsy specimens showed mild structural variants but no evidence of malignancy; therefore, diagnostic treatment was carried out. Under the adequately informed consent, an endoscopic submucosal dissection (ESD) was performed. Microscopically, a 7-mm-diameter tumor was composed of irregularly-branched neoplastic glands covered with non-neoplastic foveolar epithelium (**Fig. 2a**). The tumor cells exhibited mildly enlarged atypical nuclei with occasional cells showing oxyntic cytoplasm mimicking fundic glands cells, which invaded approximately 0.32-mm into the submucosal layer while there was no lymph-vascular invasion (**Fig. 2b** and **c**). Histological

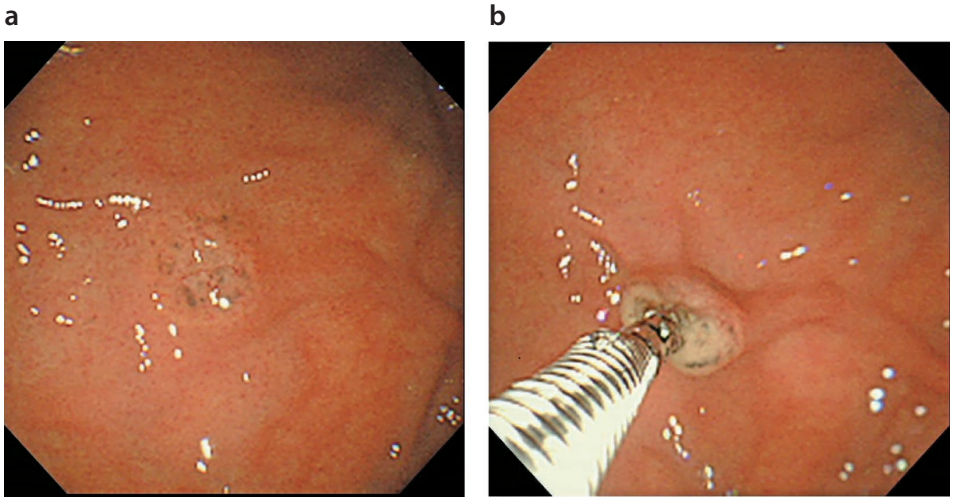

Fig. 1. Endoscopic Findings (Case 1)

(a) Endoscopic examination revealed a flat elevated, 7-mm-diameter, smooth, whitish, and SMT-like lesion in the fornix. Branched dilated vessels and pigmentation were also observed at the surface of the lesion.
(b) The tumor was soft, when grasped with forceps.

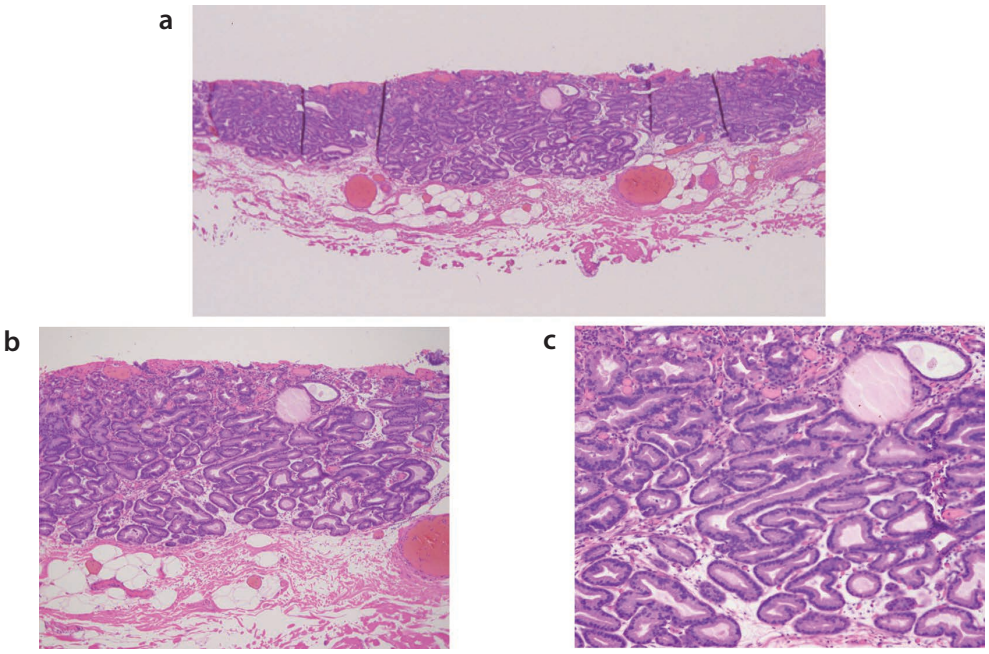

Fig. 2. Histopathologic Features of the ESD Specimen (H&E Staining)

(a) Low magnification showing a 7-mm-diameter tumor located in the deep mucosal layer covered with the non-neoplastic foveolar epithelium invading into the submucosal layer approximately 0.32 mm and no lymph-vascular invasion.
(b) Low magnification image showing irregularity branched neoplastic glands.
(c) High magnification image. The tumor cells exhibited mildly enlarged atypical nuclei with occasional cells showing oxyntic cytoplasm mimicking fundic glands cells.

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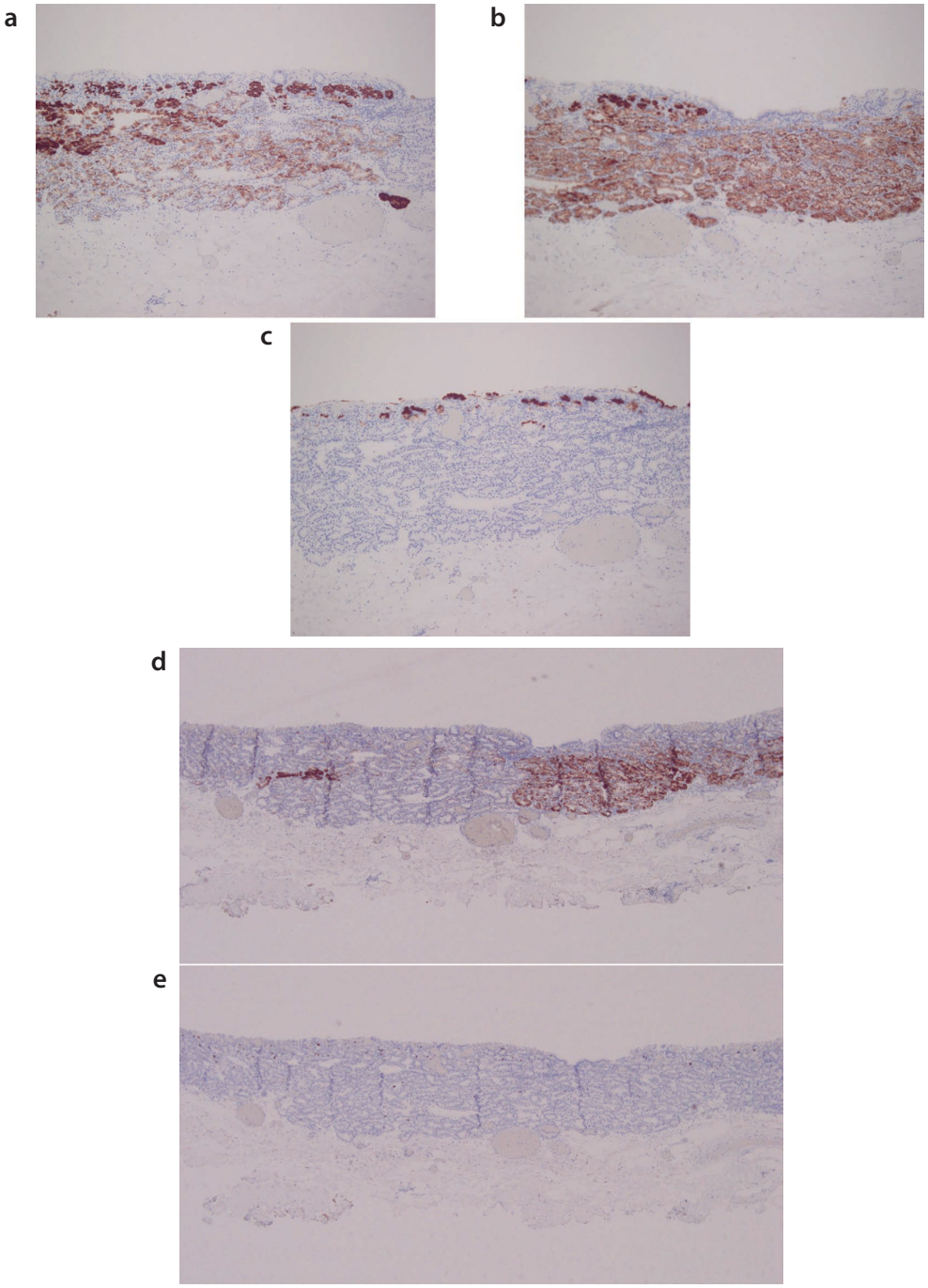

Fig. 3. Immunohistochemistry Demonstrated that the Neoplastic Glands Were Diffusely Reactive for MUC6 (a) and Pepsinogen-I (b), Negative for MUC5AC (c), Partially Positive for Synaptophysin (d), and Negative for Chromogranin A (e)

examination confirmed the diagnosis of low-grade well-differentiated adenocarcinoma. Immunohistochemistry demonstrated that the neoplastic glands were diffusely reactive for MUC6 and pepsinogen-I and non-reactive for MUC5AC (**Fig. 3a**, **b**, and **c**), confirming a gastric phenotype. These results confirmed the diagnosis of LG-WDA-G; specifically, gastric adenocarcinoma of the fundic gland type (GA-FG).

Case 2

A 49-year-old man, who had no history of eradication therapy and was tested negative for serum *H-pylori* antibody, underwent EGD screening. The examination revealed a gentle protrusion, measuring 7-mm in diameter at the greater curvature of the fornix with no atrophic change in the mucosa (**Fig. 4a**). Although this lesion was observed on X-ray 10 years earlier (**Fig. 5**), its shape and size had not significantly changed during

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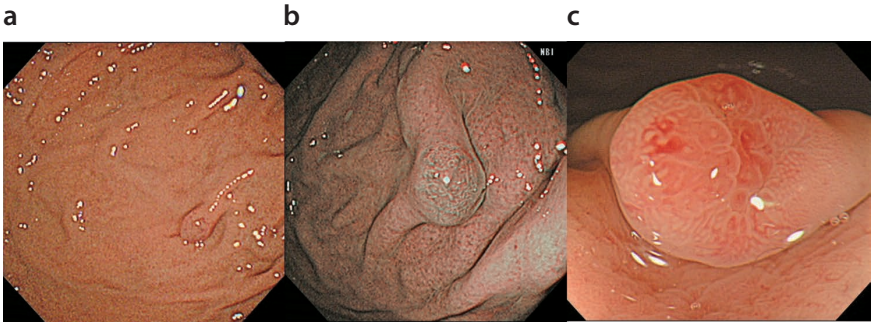

Fig. 4. Endoscopic Findings (Case 2)
(a) Endoscopic findings revealed a gentle protrusion, measuring 7-mm in diameter at the greater curvature of the fornix.
(b) Endoscopy with narrow band imaging (NBI) revealed no clear demarcation line (DL), and dilated-branched vessels and prolongations of intervening part between the crypts on the surface of the lesion.
(c) Endoscopic findings after biopsy revealed indistinct DL, dilatation of crypt opening, and dilatation of intervening part between the crypts.

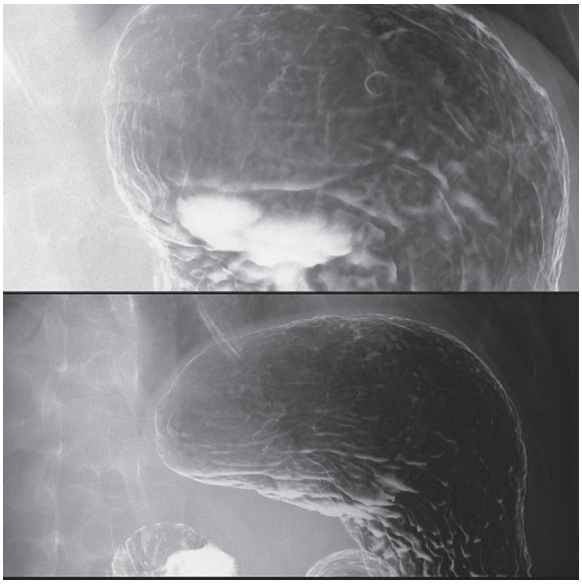

Fig. 5. X-ray Findings Are a Clear Circumference but Partially Unclear Border, Indicating the Tumor Has a Gentle Border Partly Like SMT

the ten years. The annual X-ray or endoscopic findings had been associated with fundic gland polyp. Endoscopy with narrow band imaging (NBI) revealed no clear demarcation line (DL), and proliferation of dilated vessels or prolongations of the intervening part between the crypts on the surface of the lesion (**Fig. 4b**). Biopsy specimens revealed adenocarcinoma, and therefore an ESD was performed. Histologically, a 2-mm-diameter tumor was located in the deep mucosal layer covered with the non-neoplastic foveolar epithelium, formed by irregularly shaped glands composed of slightly atypical glandular cells resembling fundic glands cells (**Fig. 6a** and **b**). These cells invaded the submucosa to approximately 0.3-mm while no lymph-vascular invasion was detected. Histological examination confirmed the diagnosis of low-grade well-differentiated adenocarcinoma. Immunohistochemistry demonstrated that the neoplastic glands were diffusely reactive for MUC6 and pepsinogen-I (**Fig. 7a** and **b**) and nonreactive for MUC2 and MUC5AC (**Fig. 7c** and **d**), confirming a gastric phenotype. These results confirmed the diagnosis of LG-WDA-G, specifically, GA-FG.

Case 3

A 66-year-old man, who had no history of eradication therapy and tested negative for serum *H-pylori* antibody, underwent EGD screening. The background mucosa revealed no endoscopic findings of atrophic gastritis. A 10-mm SMT-like elevated lesion with cen-

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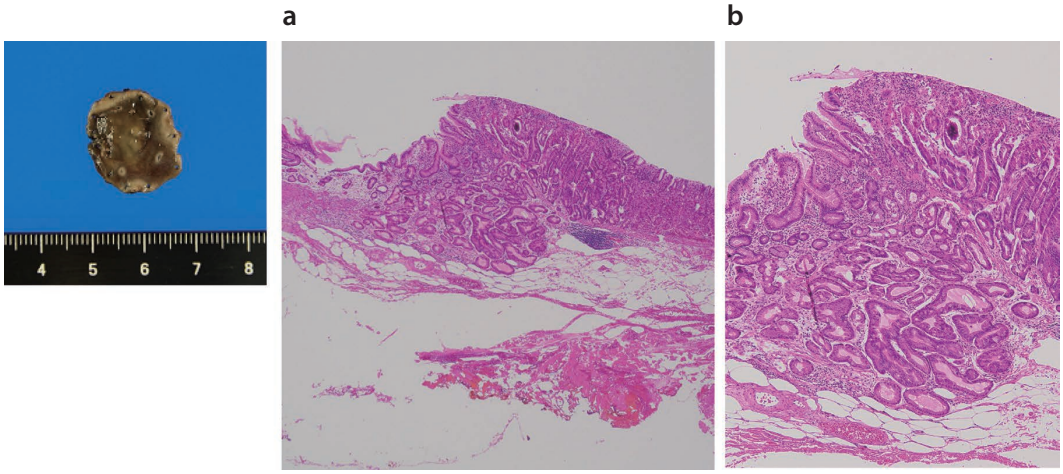

Fig. 6. ESD Specimen: The Flat Elevated Lesion Measured 7 × 7-mm

(a) Histologic slide under low magnification with H&E staining showing 2-mm-diameter tumor was located in the deep mucosal layer covered with the non-neoplastic foveolar epithelium invading into the submucosal layer approximately 0.3 mm.
(b) High magnification image shows irregularity branched neoplastic glands. The tumor cells exhibited mildly enlarged atypical nuclei with occasional cells showing oxyntic cytoplasm mimicking fundic glands cells.

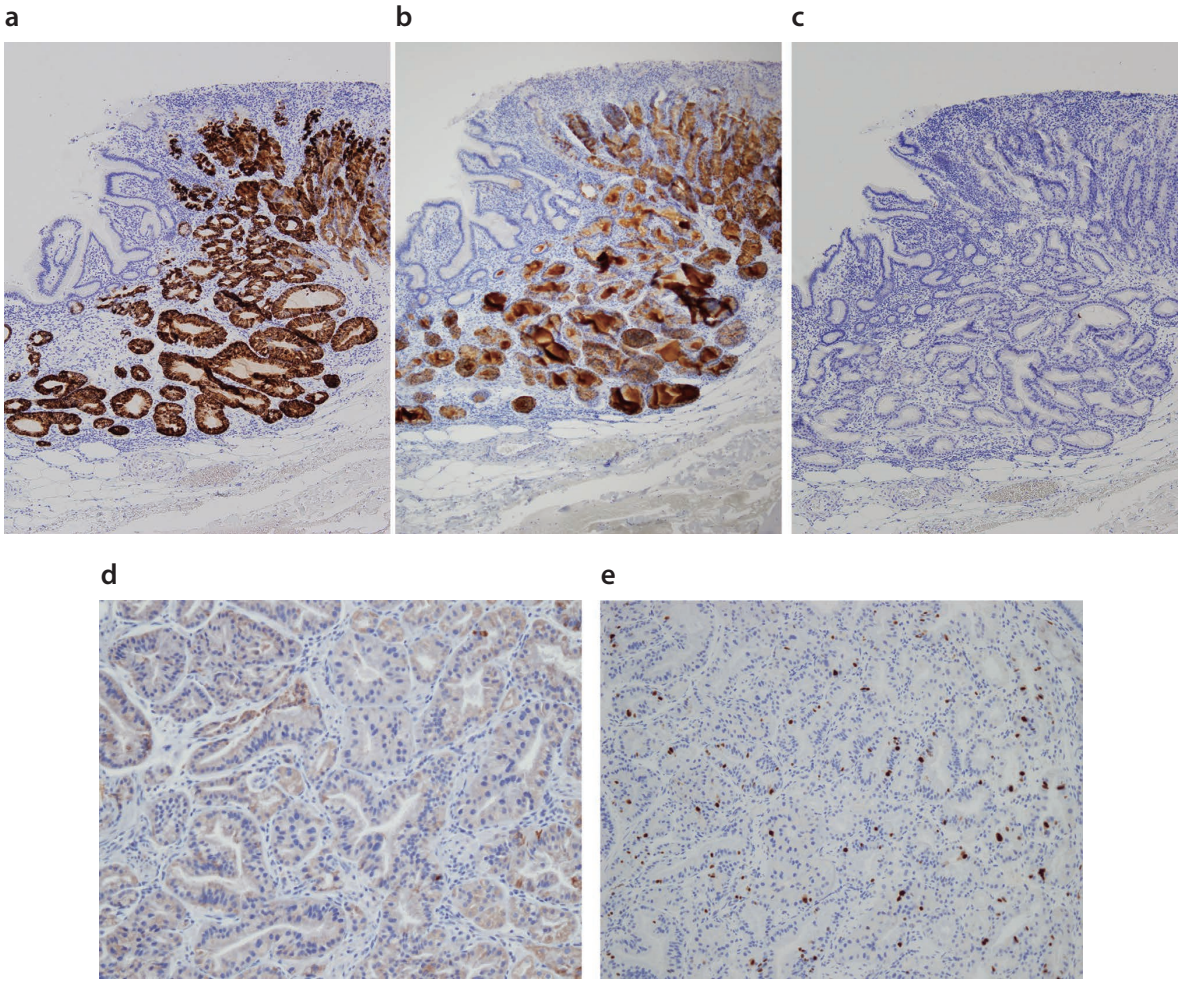

Fig. 7. Immunohistochemistry Demonstrated That the Neoplastic Glands Were Diffusely Reactive for MUC6 (a) and Pepsinogen-I (b), Nonreactive for MUC2 (c) and MUC5AC (d), and Low Labeling Index of Ki-67 (e)

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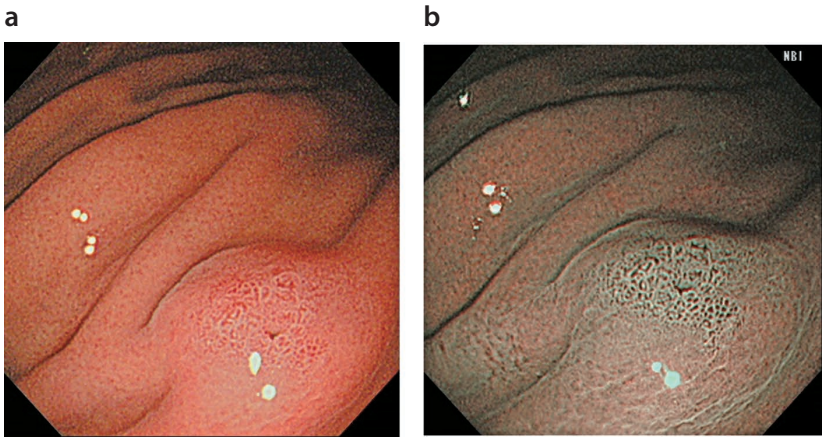

Fig. 8. Endoscopic Findings (Case 3)

(a) Endoscopic findings show a 10-mm SMT like elevated lesion with central erosion surrounding reddish mucosa on the greater curvature of the middle gastric body.
(b) Endoscopy with NBI findings shows no clear DL, and prolongations of intervening part between the crypts on the surface of the lesion.

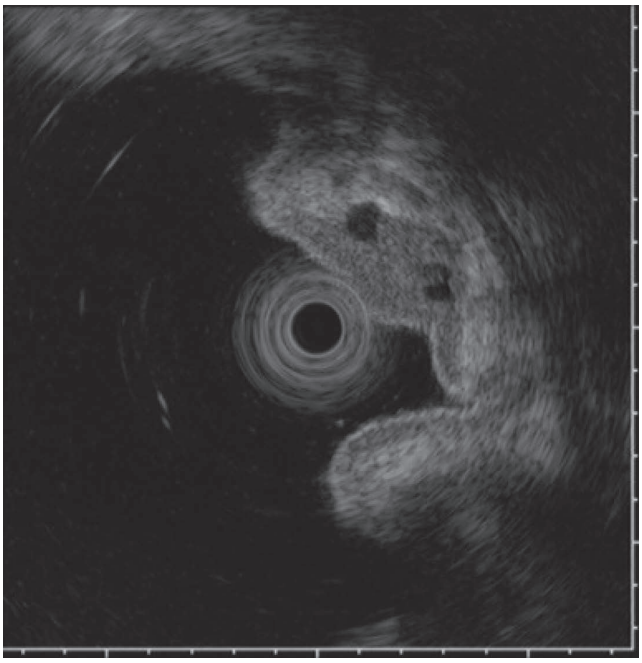

Fig. 9. Endoscopic Ultrasonography (EUS) Findings Show Isoechoic Tumor with Several Small Echo Free Spaces in the Third Layer

tral erosion surrounding a reddish mucosa was observed on the greater curvature of the middle gastric body (**Fig. 8a**). Endoscopy with NBI revealed no clear DL, and prolongations of the intervening part between the crypts were also observed at the surface of the lesion (**Fig. 8b**). Biopsy specimens showed atypical glands and indefinite neoplasia. Endoscopic ultrasonography (EUS) findings showed an isoechoic tumor with several cystic legions in the submucosal layer (**Fig. 9**). The preoperative diagnosis was early gastric cancer with submucosal heterotopic gastric glands (SHGG). Under the adequately informed consent, ESD was performed. Histologically, an 11-mm-diameter tumor was located in the lamina propria mucosae covered with the non-neoplastic foveolar epithelium, formed by irregularly shaped glands with mild nuclear atypia resembling fundic glands cells (**Fig. 10a** and **b**) This tumor was partially invading the submucosal layer to 1.9-mm, spreading along several cystic lesions. Immunostaining results were positive for MUC6, pepsinogen-I, and MUC5AC (**Fig. 11a**, **b**, and **c**). These results confirmed the diagnosis of LG-WDA-G with SHGG. Additionally, distal gastrectomy was performed, revealing no residual carcinoma and no lymph node metastasis.

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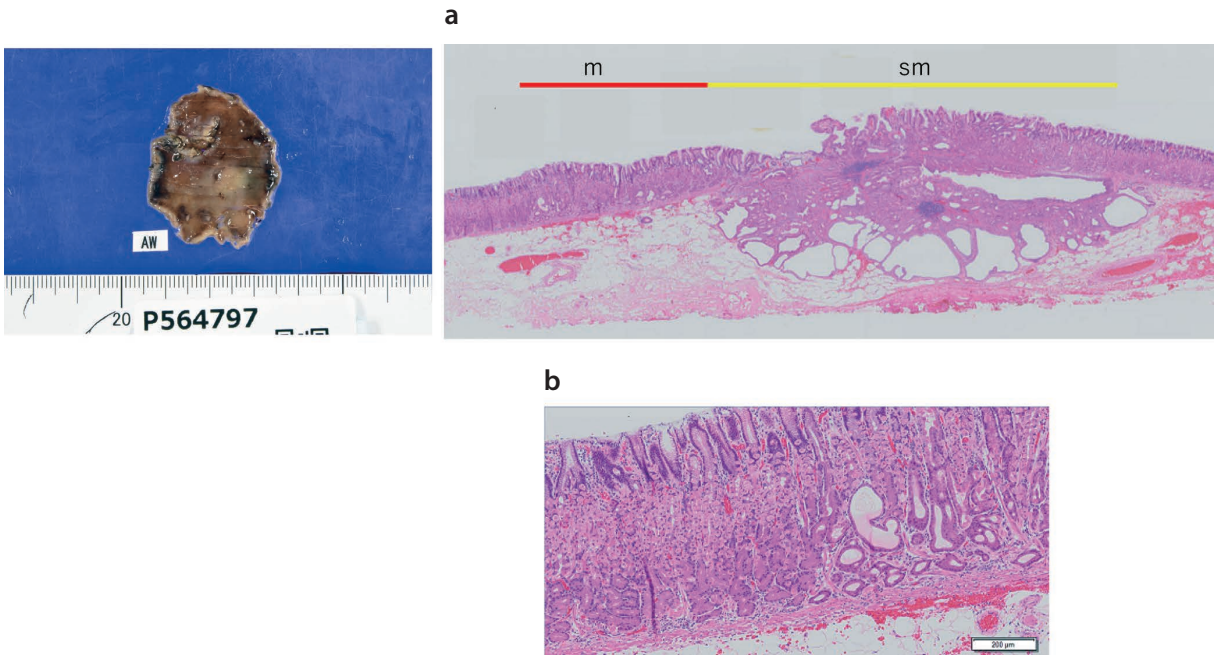

Fig. 10. ESD Specimen

(a) Histologic slide with H&E staining under low magnification showing that 11-mm-diameter tumor was located in the lamina propria mucosae covered with the non-neoplastic foveolar epithelium. This tumor was partially invading into the submucosal layer to 1,900 μm, spreading along several cystic lesions. (red bar: the tumor in situ, yellow bar: sm invasion)
(b) High magnification image shows the tumor formed by irregularly shaped glands with mild nuclear atypia resembling fundic glands cells.

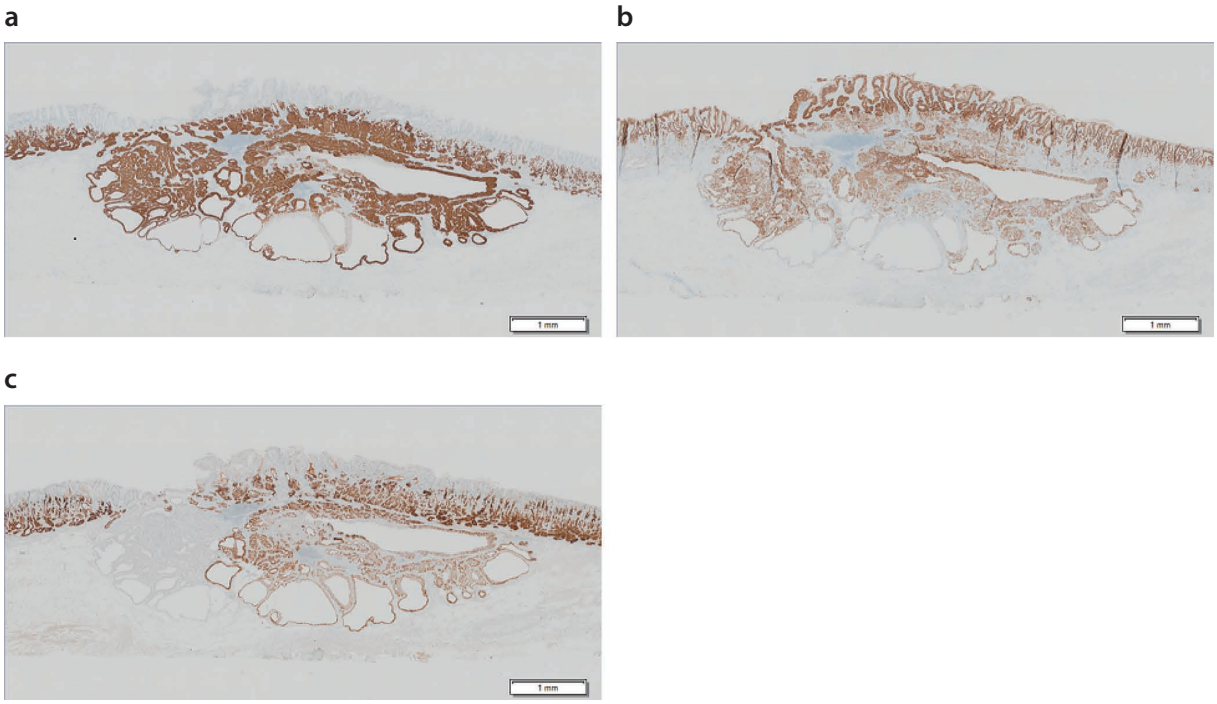

Fig. 11. Immunostaining Results Were Positive for MUC6 (a), Pepsinogen-I (b), and MUC5AC (c)

Discussion

It had been thought that differentiated adenocarcinomas originating from the intestinal metaplasia involving *H. pylori* infection had an intestinal phenotype, whereas undifferentiated adenocarcinomas originating from the gastric mucosa without the process of intestinal metaplasia had a gastric phenotype[1]. However, progress in immunohistochemical examination has revealed that some differentiated adenocarcinoma had a gastric phenotype[2].

In the three cases presented in this study, the background mucosa revealed no endoscopic findings of

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atrophic gastritis, while serum test results were negative for *H. pylori* antibody; thus, the stomach was considered to be uninfected by *H. pylori*. Moreover, these three cases presented a subepithelial or SMT-like appearance and immunohistochemical findings revealed LG-WDA-G. Immunohistochemical analysis using the following biomarkers is important for diagnosis of gastric phenotype: MUC6 for mucous neck-cells; MUC5AC for foveolar cells and pepsinogen-I for chief cells. Mucin phenotypes are assessed based on the expression of gastric-type markers such as MUC5AC and MUC6, and intestinal-type markers such as MUC2 and CD10[3].

Both cases 1 and 2 were diagnosed as GA-FG, composed of cells resembling the fundic gland cells, and positive for pepsinogen-I and MUC6[4], categorized as purely a gastric phenotype. In contrast, in case 3, not only MUC6 and pepsinogen-I, but also MUC5AC were diffusely expressed in the tumor. GA-FG with foveolar differentiation was previously reported as gastric adenocarcinoma of the fundic gland mucosa type (GA-FGM), which was thought to be a variant of GA-FG[5].

GA-FG is a subtype of LG-WDA-G with fundic glands cells differentiation, which was proposed as a novel disease concept in 2010[4]. GA-FG is thought to originate from the fundic gland region without chronic gastritis or intestinal metaplasia[6]. The Japanese Classification of Gastric Carcinoma (JCGC) was revised in 2017 and GA-FG was newly added as a special type[7]. The cells in these tumors show chief, parietal, or mucous neck-cell differentiation and typically mixed at various proportions[8]. GA-FG accounts for just 1.6% of all gastric adenocarcinomas[9].

Macroscopically, about three-quarters of GA-FG are recognized by an elevated shape, especially an SMT-like shape[9]. These tumors are usually located in the upper third of the stomach and arise from the deep layer of the gastric mucosa[6]. Ueyama *et al.*[9] reported that the most common features of GA-FG on conventional endoscopy were: 1) SMT shape, 2) whitish color, 3) dilated vessels with branching structure and 4) background mucosa without atrophic change. Miyazawa *et al.*[10] suggested that a possible reason for the macroscopic similarity of GA-FG to SMT is that GA-FG originates from the deep layer of the gastric mucosa. Fujii *et al.* [11] suggested that the faded appearance was caused by atrophy in the foveolar epithelium above cancer tubules. Vasodilation and branched vessels on the tumor surface are other characteristics of GA-FG, attributed to the displacement of surface vessels by tumor tissue followed by congestion[9,10]. In case 1, the tumor was of a whitish color appearance and had dilated vessels with branching structure and pigmentation on the surface. Some GA-FGs may be accompanied by a pigmentation localized within the lesion. This pigmentation may be a characteristic feature of GA-FG, and focusing on such pigmentation may enable early detection of the tumor[12]. An SMT-like elevated shaped GA-FG with whitish or yellowish color should be distinguished from a neuroendocrine tumor. It is reported that neuroendocrine tumors have a solid appearance, whereas GA-FG has a soft appearance[9]. In case 1, the tumor turned out to be soft when grasped with forceps, this soft appearance can be useful as a discriminating feature between the two types of lesions. Histological features of GA-FG resemble those of neuroendocrine tumor: both tumors comprise small round tumor cells and originate from the deep mucosal layer[6]. Although it is a little bit difficult to distinguish between the two tumors using a conventional hematoxylin and eosin (H&E) staining, immunohistochemical examination is useful for it[6]. These two types of lesions can be easily distinguished using immunohistochemical staining with chromogranin A and synaptophysin, which are expressed in the neuroendocrine tumor, but it should be noted that these markers may also be positive in GA-FG[4,13]. In case 1, immunostaining results were positive for pepsinogen-I and MUC6, partially positive for synaptophysin, and negative for chromogranin A (**Fig. 3 d** and **e**).

In case 2, although this lesion was detected 10 years ago, radiographic or endoscopic findings pointed at fundic gland polyp (FGP). Because FGP resembles normal fundic gland cells and has mild atypia, GA-FG can be misdiagnosed as FGP[4,14], especially in X-ray diagnosis. In case 2, X-ray findings were similar to those of FGP, which usually appear clear in the entire circumference of the tumor boundary. However, in case 2, a clear circumference with a partially unclear border were observed, indicating the tumor had a gentle border partly like the SMT.

Endoscopy with NBI can be useful for the differential diagnosis of GA-FG and FGP, and clarifying the absence of DL or presence of vasodilation and branched vessels at the tumor surface[9–11]. In case 2, the endoscopy with NBI revealed an absence of DL and dilatation of the intervening part between the crypts. These features were presented due to the location of the tumor origin and congestion by the pressure originating from the tumor[15]. Although magnifying endoscopy with NBI (ME-NBI) is also useful for detecting GA-FG from the surface findings, including indistinct DL, dilatation of crypt opening, dilatation of intervening part between the crypts and microvessels without distinct irregularity[15], evaluation with ME-NBI may be used to assist, but not to make an accurate diagnosis of GA-FG[11]. The reason being that since the GA-FG tumor is not exposed on the surface, specific features of the early gastric adenocarcinoma such as, the presence of the DL, irregular microsurface and microvascular patterns may

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not be found[10]. A biopsy may be needed for a definite diagnosis to be done using the immunohistochemically staining. It is crucial to obtain an adequate amount of tissue because the tumorous tissue of GA-FG is usually located in the deep mucosal layer[6].

Case 3 was diagnosed as LG-WDA-G with SHGG. Endoscopic findings revealed an SMT-like elevated lesion with central erosion surrounding reddish mucosa, which were a trigger to find the lesion. Endoscopy with NBI findings, including no clear DL and prolongations of the intervening part between the crypts, were also useful to detect this lesion. SHGG can present as elevated lesions covered with normal mucosa such as SMT in EGD[16]. In the case of gastric cancer originated from SHGG it is difficult to diagnose this lesion, because cancer exists at submucosa, and cancer components are not exposed on the surface[17]. In case 3, as biopsy specimens did not reveal malignancy, EUS findings led to a diagnosis of a gastric cancer with SHGG. EUS is considered a useful modality for both detecting SHGG and judging the depth of lesion invasion, because it can reveal hypoechoic scattered cystic lesions and isoechoic mass in the submucosal layer[16]. SHGG is a rare entity characterized by the ectopic proliferation of gastric glandular elements in the lamina propria. SHGG is thought to arise from gastric glands existing congenitally in the submucosa, or from aberration of the epithelium into the submucosa as a result of repeated erosion and regeneration of the mucosa[17,18]. Although SHGG is considered a benign disease, close follow-up by endoscopy is recommended because a few cases of gastric carcinogenesis associated with SHGG have been reported in 3.0–20.1% of gastric cancer cases[18–20].

Submucosal invasion, which is one of the distinctive pathological findings of GA-FG, was identified in more than half of the resected lesions despite their small size[21]. In other words, because GA-FG is generated from the deep mucosal layer, it easily invades into the submucosal layer. Although no specific treatment strategy has been established, GA-FG is considered to be an indication of endoscopic resection because of its small tumor size and benign biological behavior[6], including no overexpression of p53 protein or a low labeling index of Ki-67[4,9,10,14]. In case 2, no morphologic changes were observed over the 10 years; the tumor remained within the submucosal layer with no lymph-vascular invasion and low labeling index of Ki-67 (**Fig. 7e**). Our observation in this case suggests that GA-FG may have had a low-grade malignancy.

On the other hand, in case 3, the tumor was invading into the submucosal layer significantly along SHGG, and expressed MUC5AC diffusely. Ueyama *et al.*[4] speculated that MUC5AC is only expressed in advanced GA-FG lesions with a large diameter and heavy submucosal invasion, suggesting that cell differentiation changes from the fundic gland type to the foveolar type during disease progression. Recently, a case of GA-FG, which had a transformation into aggressive cancer with MUC5AC expression and LN metastasis, was reported[22]. Therefore, even though most GA-FG tumors grow slowly, careful follow-up alone cannot be recommended. Case 3 might be the GA-FGM, which is thought to be a variant of GA-FG, although its character is unknown. Further investigation is needed.

In conclusion, it is necessary for endoscopists to pay careful attention to the existence of these types of gastric adenocarcinomas with SMT-like appearance during routine examinations.

Acknowledgments

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Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Nakamura K, Sugano H, Takagi K: Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. Gan 1968; 59: 251–258.
2. Kabashima A, Yao T, Sugimachi K, *et al.*: Gastric or intestinal phenotypic expression in the carcinomas and background mucosa of multiple early gastric carcinomas. Histopathology 2000; 37: 513–522.
3. Tsukashita S, Kushima R, Bamba M, *et al.*: MUC gene expression and histogenesis of adenocarcinoma of the stomach. Int J Cancer 2001; 94: 166–170.
4. Ueyama H, Yao T, Nakashima Y, *et al.*: Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. Am J Surg Pathol 2010; 34: 609–619.
5. Tanabe H, Iwashita A, Ikeda K, *et al.*: Histopathological characteristics of gastric adenocarcinoma of fundic gland type. Stomach and Intestine 2015; 50: 1469–1479. (in Japanese)
6. Miyazawa M, Matsuda M, Yano M, *et al.*: Gastric adenocarcinoma of the fundic gland (chief cell-predominant type): a review of endoscopic and clinicooathological features. World J Gastroenterol 2016; 22: 10523–10531.
7. Japanese Gastric Cancer Association (ed): Japanese Classification of Gastric Carcinoma, 15th ed., Kanehara Shuppan, Tokyo, 2017. (in Japanese)
8. Kushima R, Sekine S, Matsubara A, *et al.*: Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. Pathol Int 2013; 63: 318–325.
9. Ueyama H, Matsumoto K, Nagahara A, *et al.*: Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). Endoscopy 2014; 46: 153–157.

Advance Publication: Ningen Dock International
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10. Miyazawa M, Matsuda M, Yano M, *et al*.: Gastric adenocarcinoma of fundic gland type: five cases treated with endoscopic resection. World J Gastroenterol 2015; 21: 8208–8214.
11. Fujii M, Uedo N, Ishihara R, *et al*.: Endoscopic features of early stage gastric adenocarcinoma of fundic gland type (chief cell predominant type): a case report. Case Rep Clin Patol 2015; 2: 17–22.
12. Nakagawa M, Abe M, Takada S, *et al*.: Endoscopic features of gastric adenocarcinoma of fundic gland type. Stomach and Intestine 2015; 50: 1521–1531. (in Japanese)
13. Yao T, Ueyama H, Kushima R, *et al*.: New type of gastric carcinoma-adenocarcinoma of the fundic gland type: its clinicopathological features and tumor development. Stomach and Intestine 2010; 45: 1203–1211. (in Japanese)
14. Singhi AD, Lazenby AJ, Montgomery EA: Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. Am J Surg Pathol 2012; 36: 1030–1035.
15. Ueyama H, Matsumoto K, Nagahara A, *et al*.: Tips for the endoscopic diagnosis of gastric adenocarcinoma of the fundic gland type (chief cell predominant type). Gastroenterological Endoscopy 2016; 58: 1169–1177. (in Japanese)
16. Hizawa K, Matsumoto T, Kouzuki T, *et al*.: Cystic submucosal tumors in the gastrointestinal tract: endosonographic findings and endoscopic removal. Endoscopy 2000; 32: 712–714.
17. Hagiwara T, Kakushima N, Imai K, *et al*.: Early gastric cancer with spreading to heterotopic gastric glands in the submucosa: a case report and review of the literature. Clin J Gastroenterol 2014; 7: 123–128.
18. Iwanaga T, Koyama H, Takahashi Y, *et al*.: Diffuse submucosal cysts and carcinoma of the stomach. Cancer 1975; 36: 606–614.
19. Kosugi S, Kanda T, Hatakeyama K: Adenocarcinoma arising from heterotopic gastric mucosa in the stomach. J Gastroenterol Hepatol 2006; 21: 483–484.
20. Imamura T, Komatsu S, Ichikawa D, *et al*.: Gastric carcinoma originating from the heterotopic submucosal gastric gland treated by laparoscopy and endoscopy cooperative surgery. World J Gastrointest Oncol 2015; 7: 118–122.
21. Ohara S: Clinical and endoscopic features of gastric adenocarcinoma of fundic gland type (chief cell predominant type). Gastroenterological Endoscopy 2017; 59: 413–423. (in Japanese)
22. Okumura Y, Takamatsu M, Ohashi M, *et al*.: Gastric adenocarcinoma of fundic gland type with aggressive transformation and lymph node metastasis: a case report. Journal of Gastric Cancer 2018; 18: 409–416.

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