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ORIGINAL ARTICLE

Characteristic endoscopic findings of gastric adenocarcinoma of fundic-gland mucosa type

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Abstract

Background and study aims Gastric adenocarcinoma of fundic-gland type (GA-FG) was first proposed as a new entity of gastric adenocarcinoma in 2010. Subsequently, gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM) was reported as a subtype of gastric adenocarcinoma. This study aimed to investigate the endoscopic findings of GA-FGM and to evaluate the differences between GA-FGM and GA-FG.

Patients and methods This was a single-center retrospective study. Participants were selected from patients with gastric cancer treated at Fukuoka University Chikushi Hospital, between September 2007 and May 2020. Patients histologically diagnosed with GA-FGM or GA-FG were enrolled, and endoscopic findings were analyzed in detail.

Results A total of 12 GA-FGM lesions (12 patients) and 14 GA-FG lesions (13 patients) were analyzed. The two lesion types showed similar features: most lesions were of elevated type, located in the upper stomach, and developed in the stomach without *Helicobacter pylori* infection. On conventional endoscopy using the dye-spraying method, well-demarcated fine granular areas were observed in 7 GA-FGM lesions (58%) but not in any GA-FG lesions, with a significant difference between the two groups ($P=0.001$). Magnifying endoscopy with narrow-band imaging (NBI) showed that 11 GA-FGM lesions (92%) met the diagnostic criteria for cancer according to the vessel plus surface classification system, whereas none of the GA-FG lesions met the same criteria (0%, 0/14) ($P=0.001$).

Conclusion Our results suggest that magnifying endoscopy with NBI is a potentially useful method for the diagnosis of GA-FGM.

Keywords Gastric adenocarcinoma of fundic-gland mucosa type · Gastric adenocarcinoma of fundic-gland type · Magnifying endoscopy · Narrow-band imaging · Conventional endoscopy

Abbreviations

GA-FGM	Gastric adenocarcinoma of fundic-gland mucosa type
GA-FG	Gastric adenocarcinoma of fundic-gland type
ME	Magnifying endoscopy
NBI	Narrow-band imaging

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Introduction

Gastric adenocarcinoma of fundic-gland type (GA-FG) was first proposed as a new entity of gastric adenocarcinoma by Ueyama et al. [1]. Histologically, GA-FG is an epithelial tumor with low-grade atypia showing differentiation toward fundic glands. Its superficial layer is covered with non-neoplastic mucosa, and the tumor glands with low-grade atypia densely proliferate mainly in the middle and deep layers of the mucosa of the fundic gland.

The World Health Organization classification of tumors with these histological features considers tumors remaining in the mucosa to be "oxyntic gland adenoma," while those with submucosal invasion are considered "adenocarcinoma of fundic gland type" [2]. Nevertheless, tumors remaining in the mucosa are diagnosed as intramucosal components of GA-FG based on the Japanese diagnostic criteria. Iwashita

and Tanabe et al. proposed naming tumors showing differentiation toward fundic glands and foveolar epithelium-like differentiation as gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM) [3, 4].

Ueyama et al. have reported the endoscopic features of GA-FG using white-light conventional endoscopy and magnifying endoscopy with narrow-band imaging (NBI) [5, 6]. Although several cases of GA-FGM have been reported, the endoscopic findings of GA-FGM have not been systematically investigated in consecutive patients [7, 8]. The objectives of this study were to investigate the endoscopic features of GA-FGM using white-light conventional endoscopy and magnifying endoscopy with NBI and to evaluate the differences between GA-FGM and GA-FG.

Patients and methods

Study design

This was a single-center retrospective study. This study was approved by the Institutional Review Board of the Fukuoka University Chikushi Hospital.

Patients

Inclusion criteria

The participants of this study were selected from a series of patients with gastric cancer who underwent endoscopic submucosal dissection or surgical resection at Fukuoka University Chikushi Hospital, between September 2007 and May 2020. Lesions histologically diagnosed as GA-FGM or GA-FG were included in this study.

Exclusion criteria

Patients with no available endoscopic images were excluded, because the tumor was incidentally detected during the histopathological evaluation of the resected specimen. Lesions for which endoscopic evaluation was difficult owing to the effect of biopsy were also excluded.

Methods

Definitions of GA-FG and GA-FGM

The classification of GA-FG or GA-FGM was made according to the histological and immunohistochemical criteria for low-grade atypia and differentiated gastric cancer proposed by Iwashita and Tanabe et al. [3, 4].

GA-FG Tumor cells showing differentiation toward fundic glands (i.e., cells resembling chief or parietal cells) and immunohistochemical positivity for pepsinogen-I and/or H+/K+-ATPase (Fig. 1).

GA-FGM In addition to showing the histological features of GA-FG, the tumor cells at the surface area show foveolar epithelium-like differentiation and immunohistochemical positivity for MUC5AC (Fig. 2).

Definition of the stomach without Helicobacter pylori infection

The stomach without *H. pylori* infection was defined according to the following three criteria:

1. Characteristic endoscopic findings of the stomach without *H. pylori* infection [9, 10];
2. No history of *H. pylori* eradication therapy;
3. At least two negative diagnostic tests for *H. pylori* infection (*H. pylori* IgG antibody, urea breath test, stool antigen test, rapid urease test, culture by biopsy, and microscopy).

Endoscopic procedures

Premedication and sedation All patients underwent optimum preparation. They were asked to drink a mixture of mucolytic and defoaming agents in water 30 min before the procedure [11]. The formula consisted of 20,000 U pronase (Kaken Pharmaceutical, Tokyo, Japan), 1 g sodium bicarbonate, and 10 mL dimethylpolysiloxane (20 mg/mL; Horii Pharmaceutical, Osaka, Japan) in 100 mL water. Most patients underwent sedation with intravenous injection of 3–10 mg diazepam (5 mg/mL; Takeda Pharmaceutical, Tokyo, Japan) or 2–8 mg midazolam (5 mg/mL; Sandoz, Tokyo, Japan).

Endoscopes All endoscopic procedures were performed using an electronic endoscopy system (EVIS LUCERA ELITE, EVIS LUCERA SPECTRUM; Olympus Co., Tokyo, Japan) with a high-resolution upper-gastrointestinal endoscope incorporating an optical magnifying function (GIF-Q240Z, GIF-H260Z, GIF-H290Z; Olympus Co.).

Endpoints We investigated the endoscopic features of GA-FGM using conventional white-light endoscopy and magnifying endoscopy with NBI and compared them with those of GA-FG.

Reproducibility of the findings of magnifying endoscopy with NBI for GA-FGM and GA-FG The interobserver concordance rate (between K.I. and T.K.) and the intraobserver

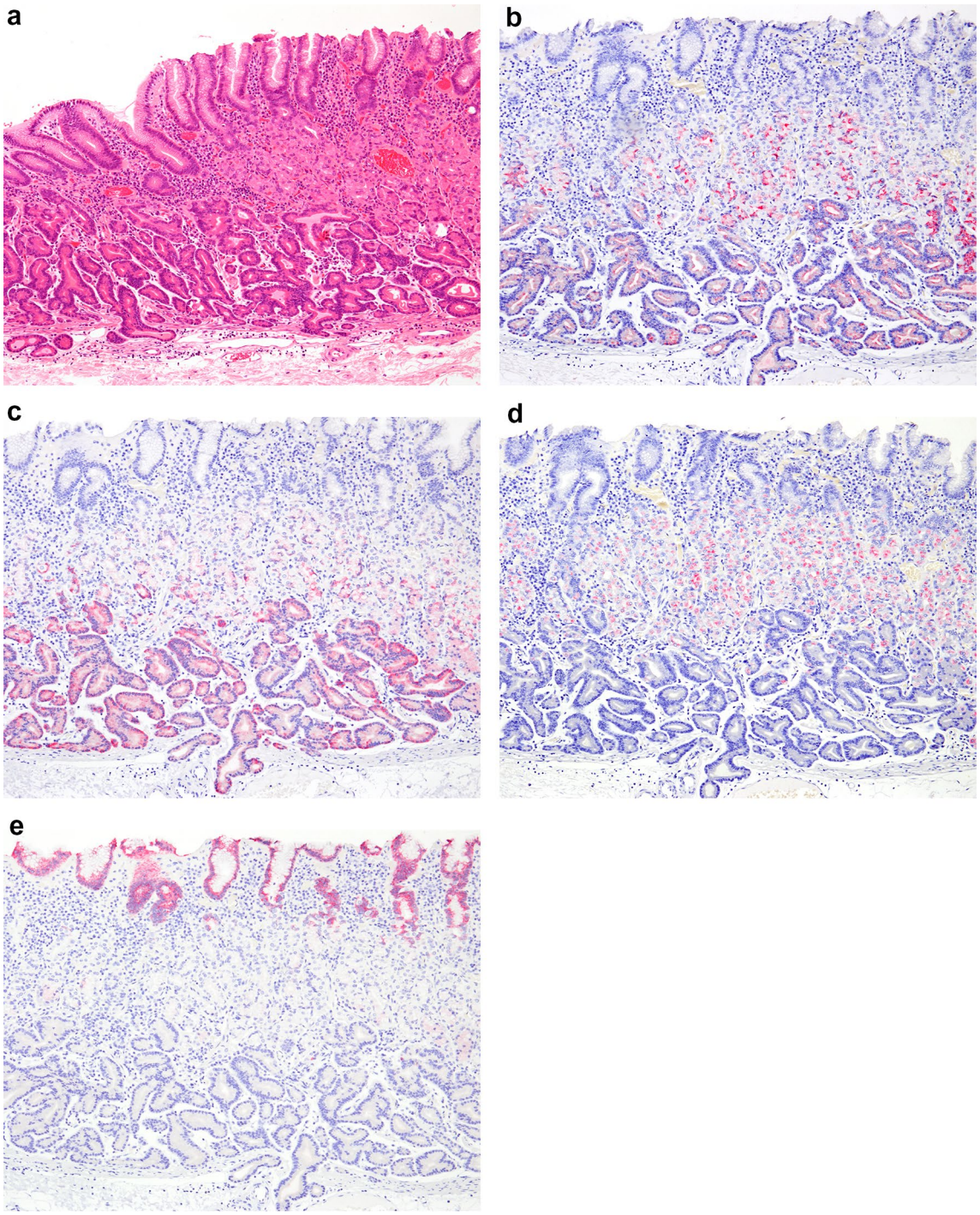

Fig. 1 Histopathological images of gastric adenocarcinoma of fundic-gland type (GA-FG). **a** Histopathological appearance with hematoxylin and eosin staining (low-power view). The superficial layer is covered with non-neoplastic mucosa, and tumor glands resembling fundic glands densely proliferate mainly in the middle and deep layers of the mucosa of the fundic gland. Minimally submucosal invasion is present. **b**–**e** Histopathological appearance with immunohistochemical staining. Pepsinogen I (**b**) and MUC6 (**c**) are diffusely expressed in tumor cells in the middle and deep layers. H+/K+-ATPase-positive cells are barely seen in the vicinity of the glandular neck (**d**). MUC5AC is expressed only in the non-neoplastic foveolar epithelia cells in the surface layer (**e**)

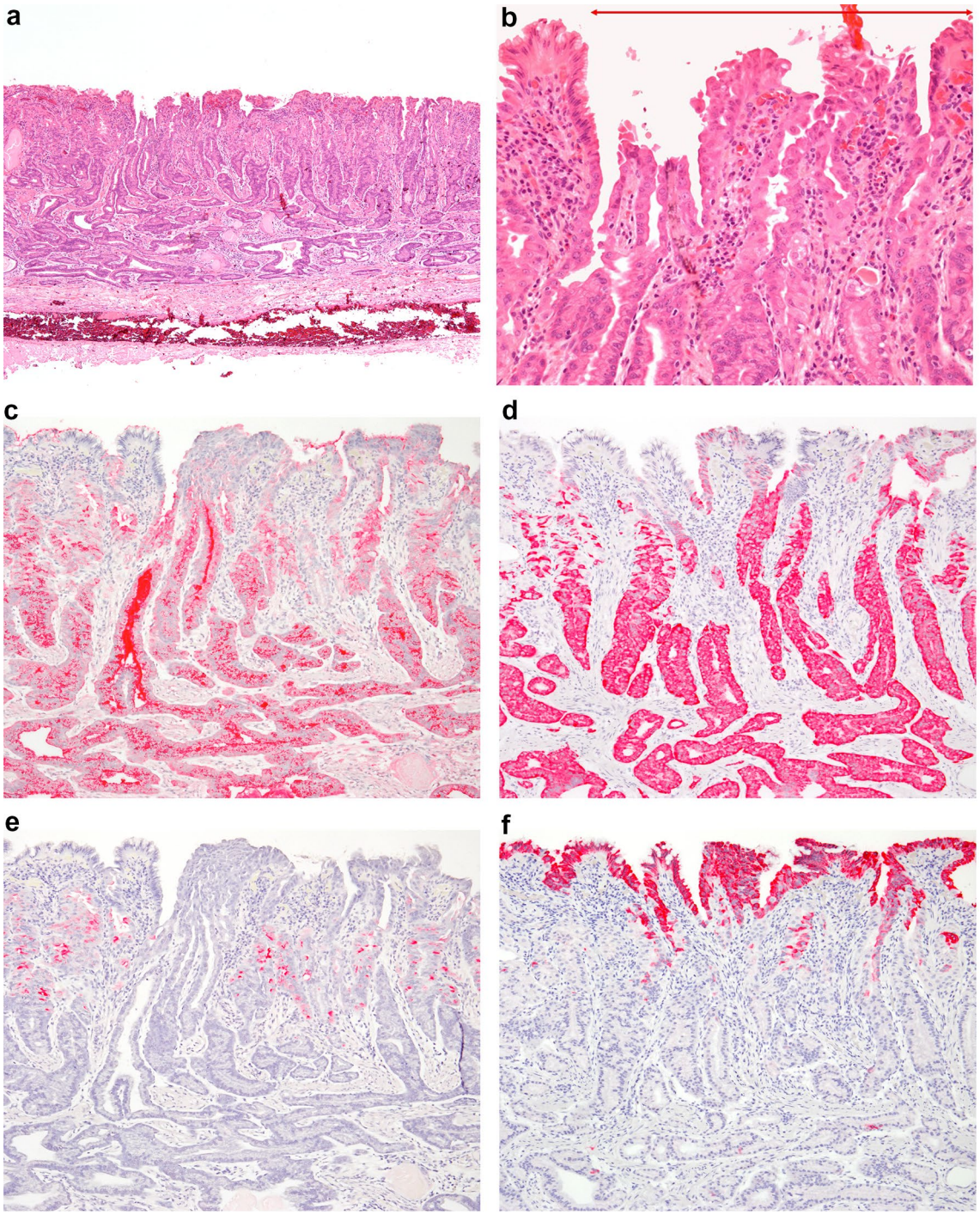

Fig. 2 Histopathological images of gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM). **a** Histopathological appearance with hematoxylin and eosin (H&E) staining (low-power view). Proliferation of tumor glands with irregular branching, and convergence in the middle and deep layers of the mucosa are also found. **b** Histopathological appearance with H&E staining (high-power view). Foveolar epithelium-like tumor glands with low-grade cytological atypia are also seen in the surface layer (red arrow). **c–f** Histopathological appearance with immunohistochemical staining. Pepsinogen I (**c**) and MUC6 (**d**) are diffusely expressed in the tumor glands except in the surface layer. By contrast, H+/K+-ATPase-positive cells are distributed in the vicinity of the glandular neck (**e**). In addition, MUC5AC is strongly expressed in the foveolar epithelium-like cells in the surface layer (**f**)

concordance rate (T.K.) were then assessed based on the findings of magnifying endoscopy with NBI for GA-FGM and GA-FG. Two endoscopists (K.I. and T.K.), with 12 and 10 years of experience with gastric magnifying endoscopy, respectively, separately evaluated the recorded M-NBI images arranged in a random order for GA-FG and GA-FGM. Both observers rated the same set of pictures. A second evaluation was performed 1 month later by T.K. using the same set of images that had been randomly rearranged before this repeat evaluation. No learning set was used, and no feedback was provided to either endoscopist before the second evaluation.

Statistical analysis

The mean values were compared using Student's *t* test. Prevalence comparisons between the two groups were performed using the Chi-square test or Fisher's exact test. *P* values < 0.05 were considered significant. SPSS version 21 J for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Clinicopathological features of GA-FG and GA-FGM lesions

A total of 1891 gastric cancer lesions were treated with endoscopic resection or surgical resection at our hospital between September 2007 and May 2020. Among them, 21 lesions (in 20 patients) were histopathologically diagnosed as GA-FG and 14 lesions (in 14 patients) were histopathologically diagnosed as GA-FGM. All patients who were histologically diagnosed with GA-FGM or GA-FG underwent endoscopic submucosal dissection. Of these, six GA-FG lesions (in six patients) and one GA-FGM lesion (in one patient) were excluded because of unavailability of endoscopic images (as the tumors were incidentally detected during the histopathological evaluation of the resected specimen), and 1 GA-FGM lesion (in one patient) and one GA-FG lesion (in one patient) were excluded, because endoscopic evaluation was difficult owing to the effect of biopsy. Finally, 14 GA-FG lesions (in 13 patients) and 12 GA-FGM lesions (in 12 patients) were included in the analysis.

Table 1 shows the clinicopathological features of GA-FG and GA-FGM lesions. The comparisons between the two groups showed no significant differences in age, sex, macroscopic type, location, frequency of submucosal invasion, or frequency of occurrence in the stomach without *H. pylori* infection. The mean tumor size tended to be larger in GA-FGM than in GA-FG, although the difference was not significant ($P = 0.084$). The two types of lesions showed the following similar features: elevated type lesions, location in the upper part of the stomach, and presence in the stomach without *H. pylori* infection. Histopathological analysis showed that both types of lesions often showed invasion into the submucosal layer. However, all lesions showed a submucosal invasion distance of < 500 µm. In addition, the mucosal surface of all GA-FGM lesions was partly covered with non-neoplastic foveolar epithelium (12/12, 100%).

Conventional endoscopic findings

Table 2 shows the conventional endoscopic findings of GA-FG and GA-FGM lesions. The surrounding mucosa had a regular arrangement of collecting venules without endoscopic atrophy in all lesions [9, 10] (Figs. 3a, 4a, 5a, 6a, and 7a). Comparisons of conventional endoscopic findings between the two types of lesions showed no significant differences in lesion color or frequencies of dilated branching vessels or subepithelial tumor-like elevation (Figs. 3a, 4a, 5a, 6a, and 7a). We also observed no significant differences in dilated vessel morphology or distribution. On conventional endoscopy with dye spraying, well-demarcated fine granular areas on the surface were not observed in GA-FG lesions but were observed in seven GA-FGM lesions (58%, 7/12), with a significant difference between the two groups ($P = 0.001$) (Figs. 3b, 5b, and 7b vs. Figure 6b).

The features of GA-FGM on conventional endoscopy are as follows: (1) lesion color similar to the color of the surrounding mucosa, or pale (75%, 9/12); (2) subepithelial tumor-like elevated lesion (75%, 9/12); (3) dilated branching vessels (67%, 8/12); and (4) well-demarcated fine granular areas demonstrated by the dye-spraying method (58%, 7/12).

Magnifying endoscopy with NBI findings

Table 3 shows the findings of magnifying endoscopy with NBI. Observation of the surrounding background mucosa using magnifying endoscopy with NBI showed similar features in the two lesion types. With respect to the microvascular (MV) structure, the subepithelial capillaries showed a regular polygon morphology, and the capillaries were uniform in shape and arranged regularly and distributed symmetrically, showing a honeycomb-like subepithelial capillary network pattern (Fig. 3c). Concerning the surface microstructure, the crypt opening and marginal crypt epithelium (MCE) showed an oval morphology, and they were uniform in shape, arranged regularly, distributed symmetrically (Fig. 3c). Thus, on magnifying endoscopy with NBI, the background mucosa showed a regular honeycomb-like subepithelial capillary network pattern plus a regular oval crypt opening and an oval MCE pattern, which were previously reported by Yao et al. as the findings of normal gastric glandular mucosa

Table 1 Clinicopathological features of GA-FG and GA-FGM lesions

	GA-FG ($n=14$)	GA-FGM ($n=12$)	P value
Mean age ± SD (years)	66.9 ± 12.5	69.9 ± 13.2	0.269*
Sex			0.474**
Male	4 (29%)	6 (50%)	
Female	10 (71%)	6 (50%)	
Mean tumor size (range) (mm)	5.1 (1–9)	7.5 (4–15)	0.084*
Macroscopic type			0.847**
Elevated	11 (79%)	10 (83%)	
Flat or depressed	3 (21%)	2 (17%)	
Location			0.946***
Upper third	12 (86%)	11 (92%)	
Middle third	0 (0%)	1 (8%)	
Lower third	0 (0%)	0 (0%)	
Remnant stomach	2 (14%)	0 (0%)	
Depth of invasion			0.774**
Mucosa	5 (36%)	4 (33%)	
Submucosa	9 (64%)	8 (67%)	
Lymphovascular invasion			0.967**
Positive	0 (0%)	0 (0%)	
Negative	14 (100%)	12 (100%)	
H. pylori-uninfected stomach			0.981**
Positive	0 (0%)	0 (0%)	
Uninfected	11 (79%)	10 (83%)	
Post-eradication	3 (21%)	2 (17%)	

GA-FG, gastric adenocarcinoma of fundic-gland type; GA-FGM, gastric adenocarcinoma of fundic-gland mucosa type; *H. pylori*, *Helicobacter pylori*; SD, standard deviation

*Student's *t* test

**Fisher's exact test

***Chi-square test

without atrophy on magnifying endoscopy with NBI [12]. Comparison of the findings of magnifying endoscopy with NBI between the two types of lesions showed that the frequencies of demarcation line (DL), irregular MV pattern, irregular microsurface (MS) pattern, and wider MCE than the background mucosa were significantly higher in GA-FGM lesions than in GA-FG lesions ($P=0.001$, $P=0.001$, $P=0.026$, and $P=0.044$, respectively) (Figs. 3d, 5c, and 7c vs. Figs. 4b and 6c). The frequencies of dilatation of the intervening part did not differ significantly between the two lesion types (P = 0.148) (Figs. 3d and 5c vs. Figs. 4b and 6c). In GA-FG, 86% (12/14) of the lesions showed a regular honeycomb-like subepithelial capillary network pattern plus regular oval crypt opening and oval marginal crypt epithelium pattern in the normal mucosa of the gastric body. In GA-FGM, only 25% (3/12) of the lesions showed such patterns ($P=0.006$). With respect to the findings of magnifying endoscopy with NBI for GA-FGM, 92% (11/12) of the lesions met the diagnostic criteria for cancer according to the vessel plus surface (VS) classification system [13, 14]. By contrast, in the findings of magnifying endoscopy with NBI for GA-FG, no lesions were diagnosed as cancer according to the VS classification system (0%, 0/14) ($P=0.001$). These findings showed that conventional white-light endoscopy alone did not allow the differential diagnosis between GA-FGM and GA-FG, whereas magnifying endoscopy with NBI was highly efficient in differentiating between these two lesion types (sensitivity 92%, specificity 100%, and accuracy 96%).

A detailed comparison of endoscopic and histological findings of GA-FGM lesions in which a DL was observed using magnifying endoscopy with NBI showed a histological boundary between the tumor and non-tumor tissues located outside the DL in 82% of cases (9/11). The median distance (range) between the DL and histological tumor boundary was 2000 (200–3500) μm.

Table 2 Conventional endoscopy findings of GA-FG and GA-FGM lesions

	GA-FG ($n=14$)	GA-FGM ($n=12$)	P value
Color			
Red	5 (36%)	3 (25%)	0.537**
Similar to the color of background mucosa	1 (9%)	4 (33%)	
Pale	8 (55%)	5 (42%)	
Dilated branching vessels			
Present	12 (86%)	8 (67%)	0.495*
Absent	2 (14%)	4 (33%)	
Subepithelial tumor-like lesion			
Present	11 (79%)	9 (75%)	0.801*
Absent	3 (21%)	3 (25%)	
Well-demarcated fine granular areas in the surface on dye spraying			
Present	0 (0%)	7 (58%)	0.002*
Absent	14 (100%)	5 (42%)	

GA-FG gastric adenocarcinoma of fundic-gland type, *GA-FGM* gastric adenocarcinoma of fundic-gland mucosa type

*Fisher's exact test

**Chi-square test

On the basis of the above results, the features of GA-FGM on magnifying endoscopy with NBI are summarized as follows: (1) presence of DL (92%, 11/12), (2) irregular MV pattern (100%, 12/12), (3) irregular MS pattern (50%, 6/12), (4) wider MCE than the surrounding background mucosa (67%, 8/12), and (5) dilatation of the intervening part (83%, 10/12).

Reproducibility of the findings of magnifying endoscopy with NBI for GA-FGM and GA-FG

The diagnostic concordance rate between the two endoscopists for GA-FGM and GA-FG was 23/26 (89%), with a kappa coefficient of 0.75 (good). The intraobserver concordance rate for GA-FGM and GA-FG was 26/26 (100%), with a kappa coefficient of 1 (excellent), as assessed by T.K.

Discussion

In this study, 92% (11/12) of GA-FGM lesions met the diagnostic criteria for cancer according to the VS classification system. This suggests that magnifying endoscopy with NBI is useful for the diagnosis of gastric cancer in patients with GA-FGM. Conversely, none of the GA-FG lesions evaluated using magnifying endoscopy with NBI met the diagnostic criteria for cancer according to the VS classification system (0%, 0/14) ($P=0.001$), which was consistent with the study by Ueyama et al. [6]. It is considered that in GA-FG, the superficial layer is covered with a non-neoplastic epithelium; thus, there is no clear DL or significant irregularity of the MV pattern or MS pattern in the surface layer on magnifying endoscopy with NBI. Conversely, in GA-FGM, foveolar epithelium-like differentiation is present in the surface layer; thus, the cancerous lesion is evident on magnifying endoscopy. The features of GA-FGM on magnifying endoscopy with NBI are as follows: (1) presence of DL (92%, 11/12), (2) irregular MV pattern (100%, 12/12), (3) irregular MS pattern (50%, 6/12), (4) wider MCE than the surrounding background mucosa (67%, 8/12), and (5) dilatation of the intervening part (83%, 10/12). Of these five features, the first four were relatively specific to GA-FGM. In this study, all GA-FGM lesions (100%, 12/12) had an irregular MV pattern. This suggests the importance of accurate assessment of the MV structure with maximum magnification. The features of GA-FGM on conventional endoscopy include (1) a lesion color similar to that of the surrounding mucosa or a pale color (75%, 9/12); (2) a subepithelial tumor-like elevated lesion (75%, 9/12); (3) dilated branching vessels (67%, 8/12); and (4) well-demarcated fine granular areas shown by the dye-spraying method (60%, 7/12). The features of GA-FGM on conventional endoscopy differ from those of GA-FG with respect to the presence of well-demarcated fine granular areas on the surface during dye spraying ($P=0.002$). In GA-FGM, tumor glands with foveolar epithelium-like differentiation are present in the surface layer, corresponding to the well-demarcated fine granular areas on the surface. However, histological examination showed that the mucosal surfaces of all GA-FGM lesions were partly covered with non-neoplastic foveolar epithelium. This was attributed to the fact that 42% of GA-FGM did not show well-demarcated areas on dye spraying and 50% of GA-FGM did not show irregular MS patterns. In lesions with small areas of cancer tissues resembling the foveolar epithelium on the surface and a surface partly covered with non-neoplastic epithelium, the differential diagnosis between GA-FG and GA-FGM based only on the surface structure after dye spraying and MS pattern on magnifying endoscopy may be difficult. However, the results of this study suggested the potential for a differential diagnosis based on the presence of a demarcation line and irregular MV pattern using magnifying endoscopy. Therefore, the MV rather than

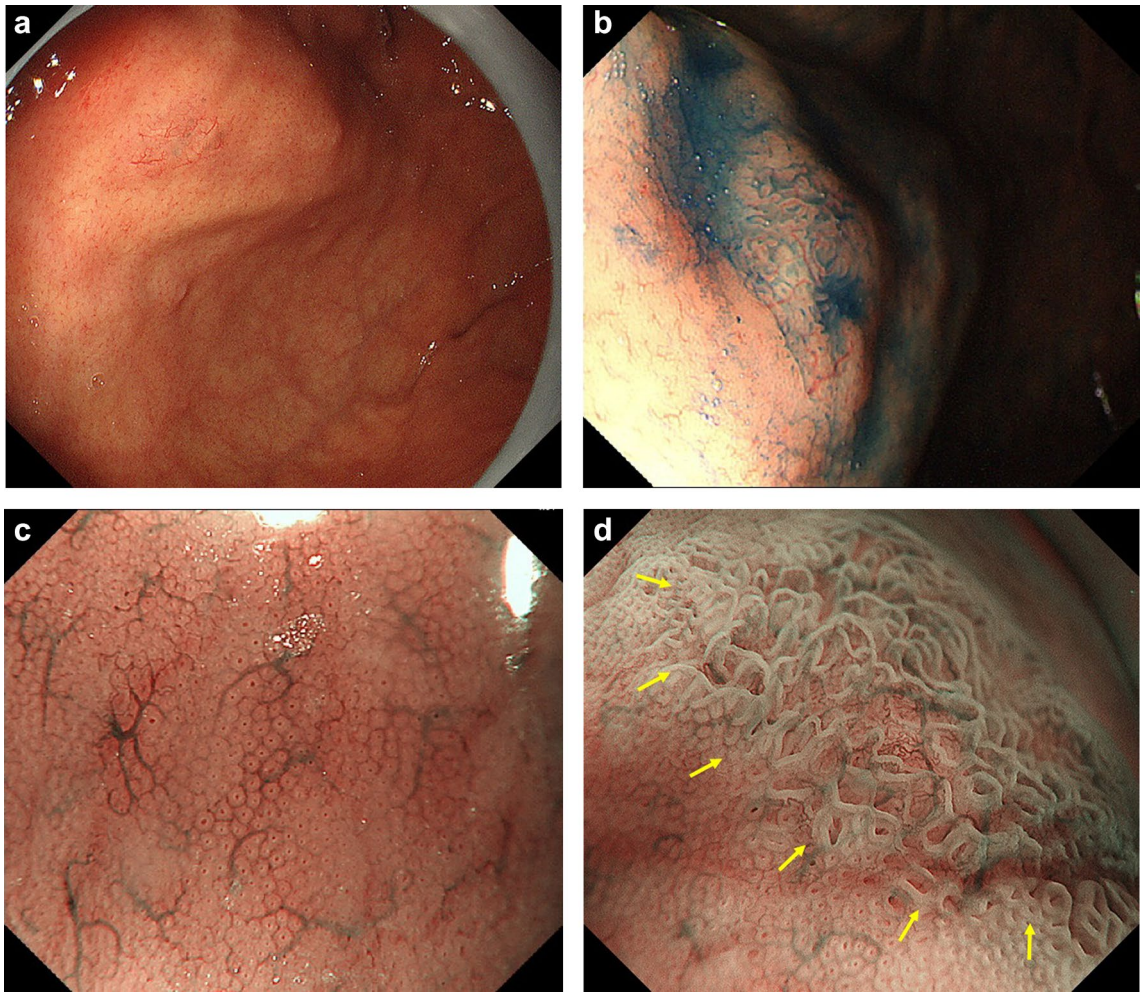

Fig. 3 Endoscopic findings of gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM). **a** Conventional endoscopic image. The surrounding mucosa shows a regular arrangement of collecting venules without endoscopic atrophy in the gastric body. A pale subepithelial tumor-like elevated lesion is observed in the posterior wall of the fundus. Dilated vessels can be seen in the elevated region. **b** Indigo carmine dye-spraying image. A granular region with clear boundaries is seen inside the elevated border of the lesion. **c** Image of the surrounding mucosa from magnifying endoscopy with narrow-band imaging (NBI). The subepithelial capillary shows a regular polygon morphology, and the capillaries are uniform in shape, arranged regularly, and distributed symmetrically, showing a honeycomb-like subepithelial capillary network pattern (regular honeycomb-like SECN pattern). The crypt opening (CO) and marginal crypt epithelium (MCE) have an oval morphology, and they are uniform in shape, arranged regularly, and distributed symmetrically. **d** Image of the lesion from magnifying endoscopy with NBI. A clear demarcation line (DL) is seen along the margin of the granular surface structure (as shown in **b**), at the top of the elevated lesion. The vessel inside the DL has an irregular open-loop morphology, and the vessels are non-uniform in shape, arranged irregularly, and distributed symmetrically. The MCE has a complex arc-shaped morphology (a ripple-like pattern), with a greater width than the background mucosa. Moreover, the MCE has a non-uniform shape, is arranged irregularly, and is distributed symmetrically. The lesion was classified as having an irregular microvascular (MV) pattern plus an irregular microsurface (MS) pattern with a demarcation line (DL) according to the vessel plus surface (VS) classification system and was diagnosed as cancer

the MS pattern is more useful for the differential diagnosis between GA-FG and GA-FGM.

In general, the diagnosis of GA-FG is difficult, because histopathological diagnosis based on biopsy specimens is often challenging, and a clear understanding of the histopathological features is mandatory [6]. Furthermore, the diagnosis of GA-FGM is based on targeted biopsy of the region involving foveolar epithelium-like differentiated cells, and the absence of a definitive diagnosis on biopsy may not be uncommon. However, this study suggests that the endoscopic diagnosis of FA-FGM is possible if a lesion has the characteristic features on conventional endoscopy, as shown in this study, and meets the diagnostic criteria for cancer according to the VS classification system using magnifying endoscopy with NBI.

DL is an important factor in endoscopic diagnosis and assessment of the extent of excision during endoscopic treatment [15–18]. However, unlike conventional epithelial

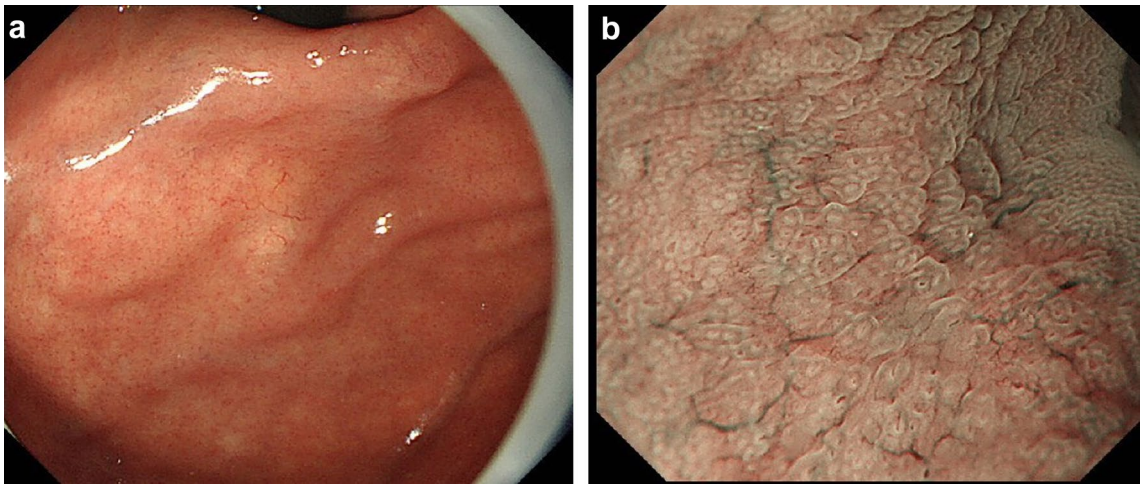

Fig. 4 Endoscopic findings of gastric adenocarcinoma of fundic-gland type (GA-FG). **a** Conventional endoscopic findings. A pale, low-elevated lesion with a gentle slope and dilated vessels in the surface of the posterior wall of the fundus are seen. **b** Image of the lesion from magnifying endoscopy with narrow-band imaging (NBI). On observation of the surrounding area, the lesion shows no marked changes in microvascular (MV) pattern or microsurface (MS) pattern, and there is no clear demarcation line (DL). The microvessel has a polygonal closed-loop morphology, and the vessels are uniform in shape, arranged regularly, and distributed symmetrically. The marginal crypt epithelium (MCE) has an oval or arc-shaped morphology and is uniform in shape, arranged regularly, and distributed symmetrically. The lesion was classified as having a regular microvascular pattern plus a regular microsurface pattern without a DL according to the vessel plus surface classification system. That is, the magnifying endoscopy findings of the lesion did not meet the diagnostic criteria for cancer

Table 3 Magnifying endoscopy with NBI findings of GA-FG and GA-FGM lesions

	GA-FG (n = 14)	GA-FGM (n = 12)	*P* value
Demarcation line			
Present	0 (0%)	11 (92%)	0.001*
Absent	14 (100%)	1 (8%)	
Irregular microvascular pattern			
Present	1 (7%)	12 (100%)	0.001*
Absent	13 (93%)	0 (0%)	
Irregular microsurface pattern			
Present	0 (0%)	6 (50%)	0.026*
Absent	14 (100%)	6 (50%)	
Wider marginal crypt epithelium			
Present	3 (21%)	8 (67%)	0.044*
Absent	11 (79%)	4 (33%)	
Dilatation of the intervening part			
Present	9 (64%)	10 (83%)	0.391*
Absent	5 (36%)	2 (17%)	

NBI narrow-band imaging, *GA-FG* gastric adenocarcinoma of fundic-gland type, *GA-FGM* gastric adenocarcinoma of fundic-gland mucosa type

*Fisher's exact test

tumors, GA-FG and GA-FGM invade subepithelial tissues horizontally; thus, the tumor is likely to be located outside the DL on the surface as observed using magnifying endoscopy. In this study, the boundary between the tumor and non-tumor tissues was located outside the DL in 82% of cases (9/11). The median distance (range) between the DL and histological tumor boundary was 2000 (200–3500) μm. Thus, we recommend that when performing endoscopic treatment of GA-FGM, the lesion should be resected at least 3500 μm from the DL or the resection line should be determined preoperatively after confirming the absence of tumor cells in at least four biopsy specimens collected from the background mucosa surrounding the tumor at the time of preoperative endoscopy. This study is clinically relevant as it is the first study to compare the features of GA-FG and GA-FGM using conventional and magnifying endoscopy.

The clinicopathological analysis showed that GA-FGM and GA-FG had similar features in that most lesions were of the elevated type, located in the upper part of the stomach, and developed in the stomach without *H. pylori* infection. GA-FG is a major subtype of *H. pylori*-negative gastric cancer [1]. This study suggests that, similar to GA-FG, GA-FGM may also be a subtype of *H. pylori*-negative gastric cancer. GA-FG has been reported to have low-grade malignancy with a good prognosis; tumor cells infiltrate the submucosal layer in the early phase of the disease, but venous invasion and lymph node metastasis are rare [1]. However, cases of GA-FGM with high-grade malignancy associated with lymph vessel and vein invasion have been reported [19]. Accordingly, it is clinically important to differentiate

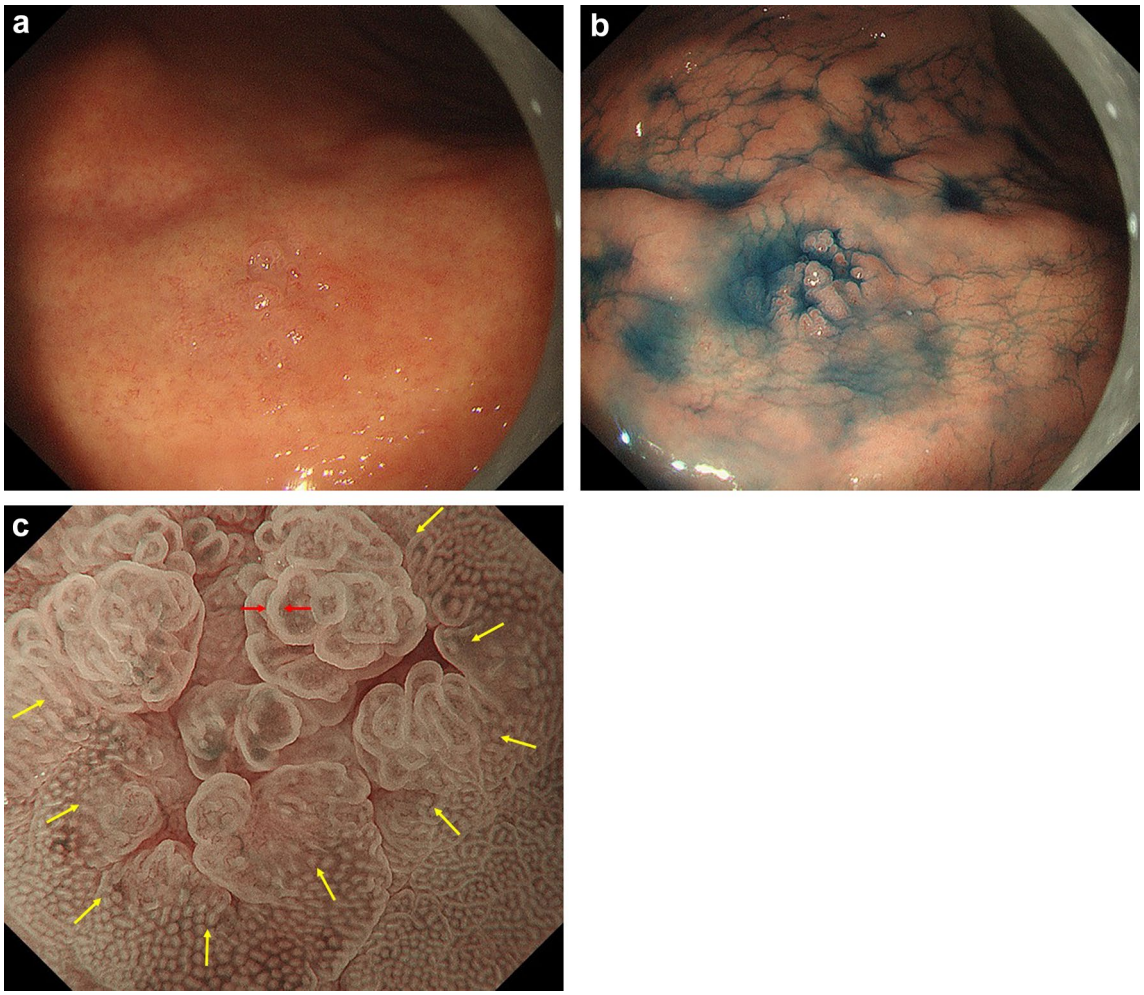

Fig. 5 Endoscopic findings of gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM). **a** Conventional endoscopic image. The lesion has a slightly red mucosa with rather indistinct boundaries in the greater curvature of the upper gastric body. **b** Indigo carmine dye-spraying image. The lesion shows slight elevation, with well-demarcated granular areas on the surface. **c** Image of the lesion from magnifying endoscopy with narrow-band imaging (NBI). On observation from the background mucosa, the elevated lesion shows marked changes both in the microvascular (MV) and microsurface (MS) patterns, and there is a clear demarcation line (DL) (yellow arrow). With respect to the MV pattern, the lesion mainly consists of microvessels with loop-like formations, and the vessels are not uniform in shape, are distributed asymmetrically, and are arranged irregularly. With respect to the MS pattern, the marginal crypt epithelium (MCE) is wider than the background mucosa (red arrow) and has a curved or oval morphology. The MCE is non-uniform in shape and is distributed asymmetrically and arranged irregularly. In addition, the intervening part is dilated. The lesion was classified as having an irregular MV pattern plus an irregular MS pattern with a DL according to the vessel plus surface classification system and was diagnosed as cancer

GA-FGM from GA-FG. In this study, the mean tumor sizes (range) of GA-FG and GA-FGM were 5.1 mm (1.0–9.0 mm) and 7.5 mm (4.0–15.0 mm), respectively. Although GA-FGM tended to be larger than GA-FG, the difference was not significant ($P = 0.084$). Furthermore, there was no difference in the endoscopic appearance between cases in this study. Detailed studies with larger sample sizes are needed to describe the clinicopathological and endoscopic features of GA-FGM to clarify clinicopathological differences between the two types of lesions. The limitations of this study were its single-center retrospective design and the small sample size. Studies in large cohorts are needed to verify the clinicopathological features and endoscopic findings of the two tumor types.

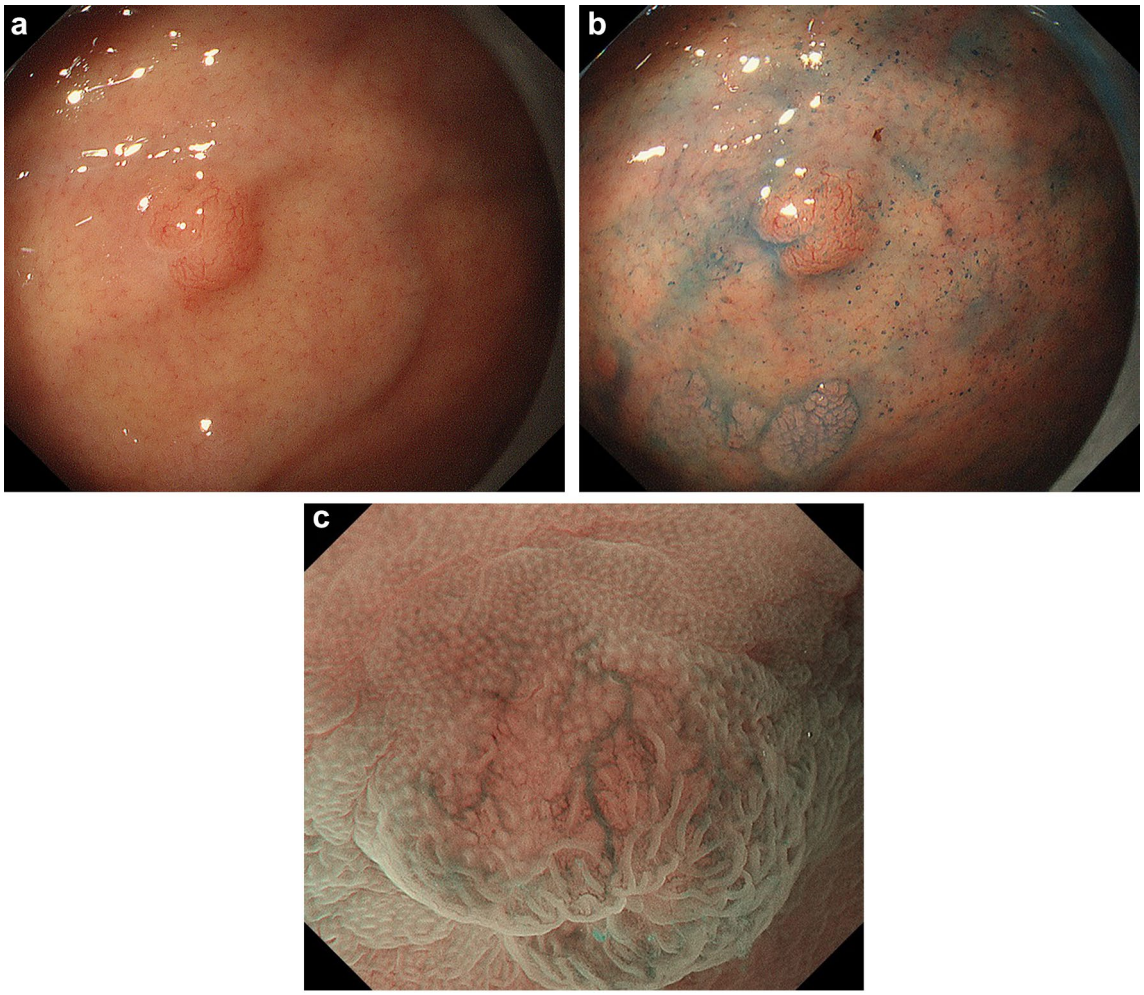

Fig. 6 Endoscopic findings of gastric adenocarcinoma of fundic-gland type (GA-FG). **a** Conventional endoscopic findings. A red low elevated lesion with a gentle slope and dilated vessels on the surface of the grater curvature of the fundus, with a biopsy scar visible at the center of the elevation. **b** Image of indigo carmine dye spraying. The lesion shows a slight elevation with a flat and smooth surface. **c** Image of the lesion using magnifying endoscopy with narrow-band imaging (NBI). Observation of the area surrounding the lesion showed no marked changes in microvascular (MV) or microsurface (MS) patterns and no clear demarcation line (DL). The central part of the figure is shown to avoid the influence of biopsy. The microvessel has a polygonal closed-loop morphology. The vessels are uniform in shape, arranged regularly, and distributed symmetrically. The marginal crypt epithelium (MCE) has an oval or arc-shaped morphology, is uniform in shape, arranged regularly, and distributed symmetrically. According to the vessel plus surface classification system, the lesion was classified as having a regular microvascular pattern plus a regular microsurface pattern without a DL. That is, the magnifying endoscopy findings of the lesion did not meet the diagnostic criteria for cancer

In conclusion, this study demonstrated the features of GA-FGM on conventional endoscopy and magnifying endoscopy with NBI. The results suggested that, in many cases, the diagnosis of GA-FGM can be obtained using magnifying endoscopy with NBI according to the VS classification system.

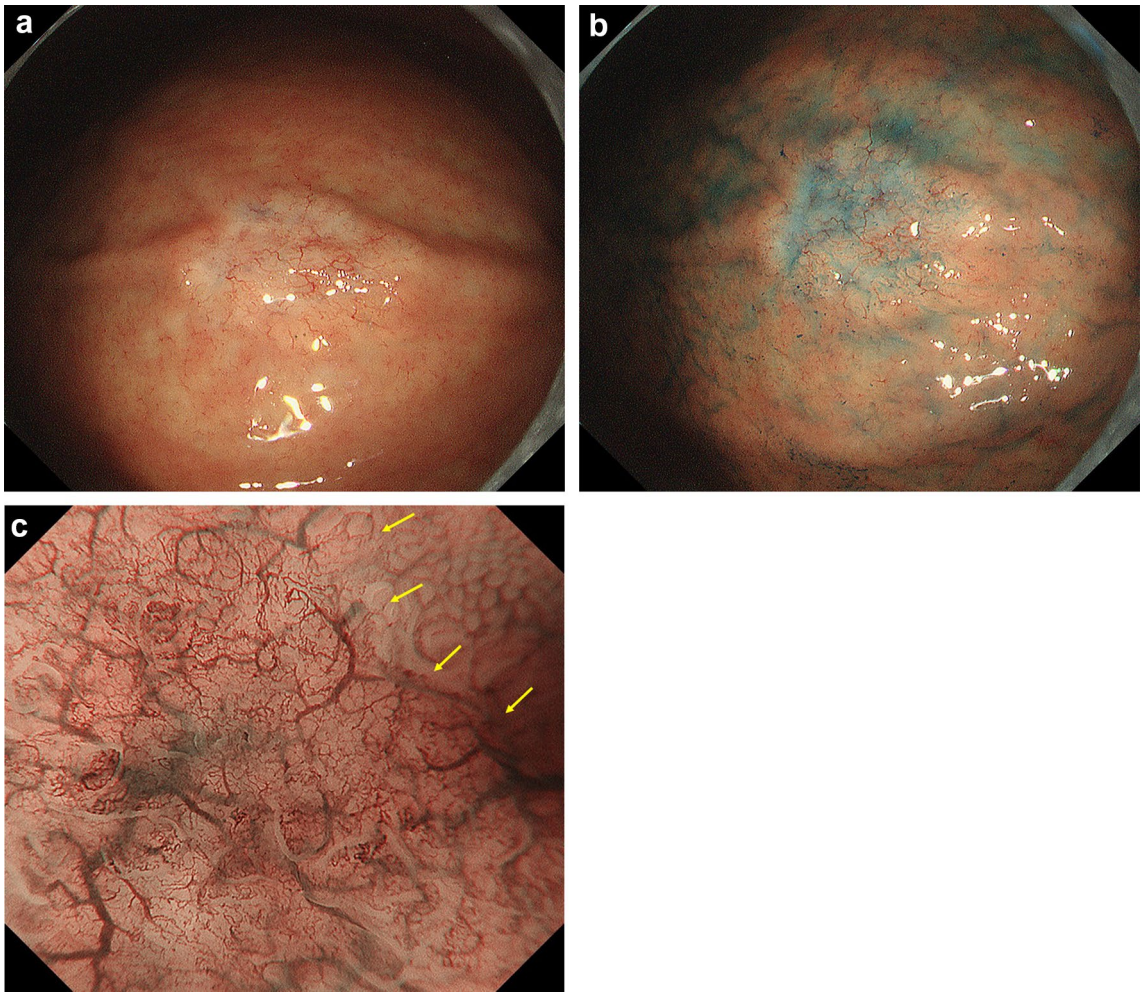

Fig. 7 Endoscopic findings of gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM). **a** Conventional endoscopic image. A pale, low-elevated lesion with a gentle slope and dilated vessels in the surface of the anterior wall of the fundus are seen. **b** Indigo carmine dye-spraying image. The lesion shows slight elevation, with well-demarcated granular areas on the surface. **c** Image of the lesion from magnifying endoscopy with narrow-band imaging (NBI). On observation from the background mucosa, the lesion shows marked changes both in the microvascular (MV) and microsurface (MS) patterns, and there is a clear demarcation line (DL) (yellow arrow). With respect to the MV pattern, the lesion consists of microvessels with open and closed loop formations, and the vessels are not uniform in shape, are distributed asymmetrically, and are arranged irregularly. With respect to the MS pattern, almost no the marginal crypt epithelium (MCE) can be visualized. The lesion was classified as having an irregular MV pattern plus an absent MS pattern with a DL according to the vessels pulse surface classification system and was diagnosed as cancer

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Declarations

Conflict of interest The authors report no potential conflicts of interest relevant to this article.

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