Gastric adenocarcinoma of fundic gland type (chief cell predominant type) with unique endoscopic appearance curatively treated by endoscopic submucosal resection

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Abstract

Gastric adenocarcinoma of fundic gland type [chief cell predominant type ; (GA-FD-CCP)] is a rare gastric cancer variant arising from non-atrophic mucosa without *Helicobacter pylori* infection in the upper third portion of the stomach. GA-FD-CCP originates deep in the mucosal layer ; hence, endoscopic lesion detection is often difficult at an early stage because of a minimal change in the mucosal surface. Here we present a 66-year-old man with an early stage of GA-FD-CCP showing characteristic endoscopic features. Esophagogastroduodenoscopy demonstrated a flat, slightly reddish area with black pigment dispersion and irregular micro-surface structure at the gastric fornix. The tumor was resected by endoscopic submucosal dissection and was pathologically diagnosed as GA-FD-CCP. Prussian blue staining revealed that the black pigment was a hemosiderin deposition. We reported a rare case of successfully treated GA-FD-CCP with black pigmentation that aided in early lesion detection. (Acta gastroenterol. belg., **2015**, 78, **336-339**).

Keywords : gastric adenocarcinoma of fundic gland type (chief cell predominant type), endoscopic submucosal resection, intratumoral hemorrhage.

Introduction

While the worldwide gastric cancer incidence has decreased swiftly over the past few decades, it remains a major mortality cause in Japan (1). A strong association is evident between *Helicobacter pylori* infection and the risk of developing gastric carcinoma (2). The decline in *H. pylori* prevalence could lead to an increase in the number of patients with *H. pylori*-negative gastric adenocarcinoma (3). Gastric adenocarcinoma of fundic gland type (chief cell predominant type ; GA-FG-CCP) has recently been identified as a novel variant of highly differentiated gastric adenocarcinoma, arising deep in the mucosal layer in the non-atrophic fundic gland mucosa without *Helicobacter pylori* infection (4). Although GA-FD-CCP exhibits submucosal invasion despite the small lesion size, neither lymphatic or venous invasion nor distant metastasis is observed. The Ki-67 labeling index of these tumors is very low, which reflects their less aggressive slow growth (4). GA-FD-CCP has a low probability of transforming into high-grade malignancy (5). However, little is known about the long-term outcome of this disease. These tumors may have a favorable prognosis that is affected by their low malignancy behavior (4,6). We report a rare case of successfully treated GA-FD-CCP with distinctive endoscopic features that aided in tumor discovery.

Case report

Annual upper endoscopic screening revealed a focal lesion without clear boundaries in the gastric fornix posterior wall. The patient was referred to our hospital for further lesion examination. Our first esophagogastroduodenoscopy (EGD) revealed a small black lesion arising from non-atrophic gastric mucosa in the posterior fornix wall (Fig. 1a). Close observation revealed a flat tumor with black pigment dispersion throughout (Fig. 1b). Histopathological analysis of gastric tumor biopsy specimens revealed atypical glands suspected, but not diagnostic, of gastric cancer (Fig. 2a). Pathological findings from the second EGD revealed adenocarcinoma comprising tumor cells forming a tubular structure. However, black pigmentation was hardly noticeable during magnifying endoscopy with narrow band imaging (ME-NBI) or endoscopic ultrasonography (EUS) conducted 3 weeks after the second EGD (Fig. 1c). ME-NBI portrayed a slightly irregular micro-surface structure and regular micro-vascular pattern around the scar after biopsy (Fig. 1d). Partial disruption of the submucosal layer was detected by EUS (Fig. 1e) ; however, the tumor did not appear to invade the submucosa. We performed endoscopic submucosal dissection (ESD) after obtaining informed consent from the patient, and we successfully removed the tumor in one piece. The histological findings of resected specimens revealed well-differentiated adenocarcinoma resembling fundic gland cells proliferated in the deeper mucosal layer (Fig. 2b). The tumor immuno-

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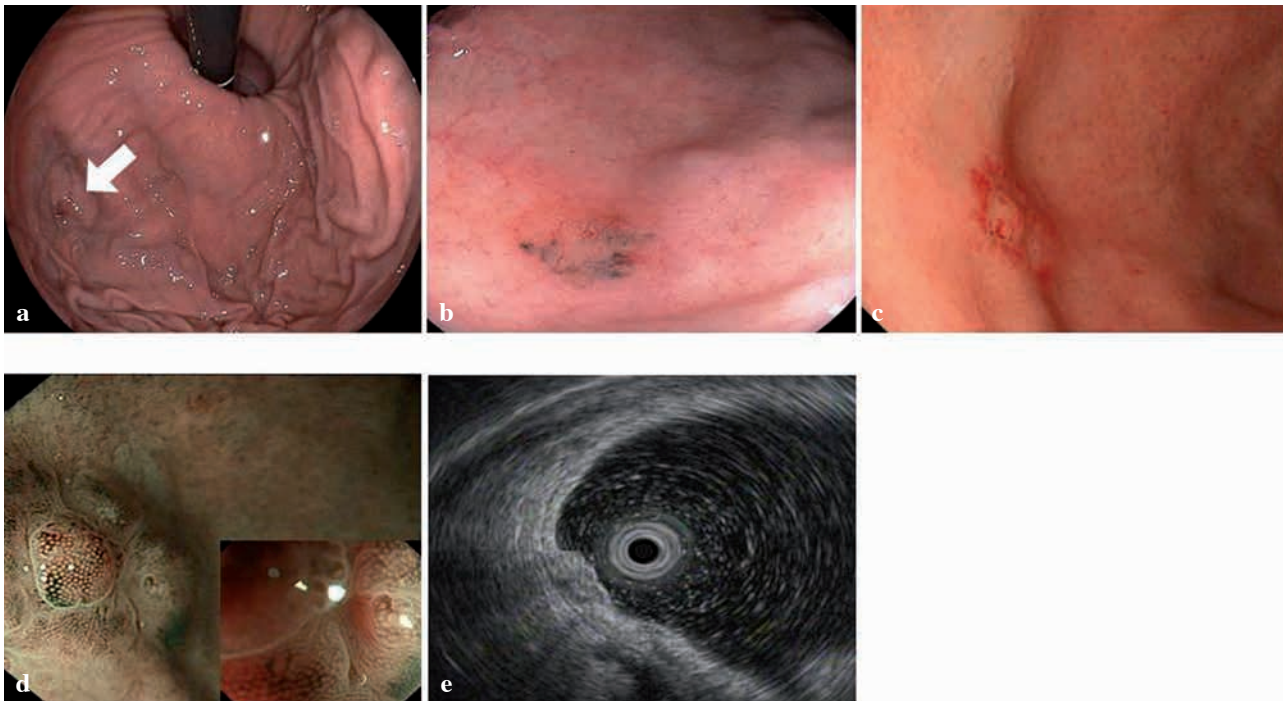

Fig. 1. — (a) Endoscopic examination (first esophagogastroduodenoscopy) revealed black pigmentation (white arrow) on the posterior wall of the greater curvature of the gastric fornix. (b) The close view presented a flat lesion with black pigment dispersion. (c) Black pigmentation was scarcely observed in the tumor at 7 weeks post initial discovery. (d) Magnifying endoscopy with narrow band imaging showed a slightly irregular micro-surface pattern and regular micro-vascular pattern around the scar after biopsy (moderate and full zoom). (e) Endoscopic ultrasonography portrayed the discontinuity in the third layer.

histochemical findings were positive for pepsinogen-I (Fig. 2c) and MUC6 (Fig. 2e) and partially positive for H^+/K^+ ATPase (Fig. 2d). The patient was determined to be *H. pylori*-negative using the rapid urease test and IgG *H. pylori* serum antibody. Prussian blue (PB) staining was performed to investigate whether the black pigmentation originated from hemosiderin. In hematoxylin and eosin (HE) stained sections, hemosiderin-laden macrophages were detected as brown granules in the corresponding area of adjacent sections stained positively with PB (Fig. 2f, 2g, 2h, 2i). However, no melanin was detected with the Fontana-Masson technique in these sections stained positively with PB (data not shown). The final pathological diagnosis of the tumor after endoscopic resection was GA-FG-CCP (m, ly0, v0, pLM(–), pVM(–), well-differentiated adenocarcinoma).

Discussion

In total, 83 GA-FD-CCP cases have been reported worldwide thus far, including 69 in Japan (4,6,7,8,9,10, 11,12). In terms of GA-FD-CCP endoscopic features, as shown in Table 1, the macroscopic tumor forms were usable in 54 cases, in which 38 cases (70.4%) consisted of protruding lesions and the remaining consisted of flat and depressed lesions (7.4% (4/54) and 22.2% (12/54), respectively). Dilated capillaries on tumors were remarkable in 18.1% (15/83) cases. Thus, the flat form with black pigmentation is considered to be a rare endoscopic appearance of GA-FD-CCP.

We observed the tumor exhibiting black pigmentation, which could serve as a starting point for GA-FD-CCP diagnosis. However, the black pigmentation was scarcely observed in endoscopic images taken 7 weeks after initial pigmentation discovery. In addition, neither blue granules from PB staining nor brown granules from HE-stained sections were observed in the biopsy tissues (data not shown). Hemosiderin pigmentation is most commonly granular- or crystalline-shaped within the stroma but not the epithelium. However, we found PB-positive cells within epithelial cells. Hemosiderin accumulation in the epithelium, lamina propria, and cytoplasm of gastric glands is reported in less than 1% of gastric biopsy specimens, the majority of which are associated with drug-induced erosive mucosal injury (13). We speculate that black pigmentation loss occurred relatively quickly because of the fast gastric mucosa turnover rate. From these results, we confirmed that the macroscopic dark pigmentation was generated from iron deposition in the mucosal epithelial layer.

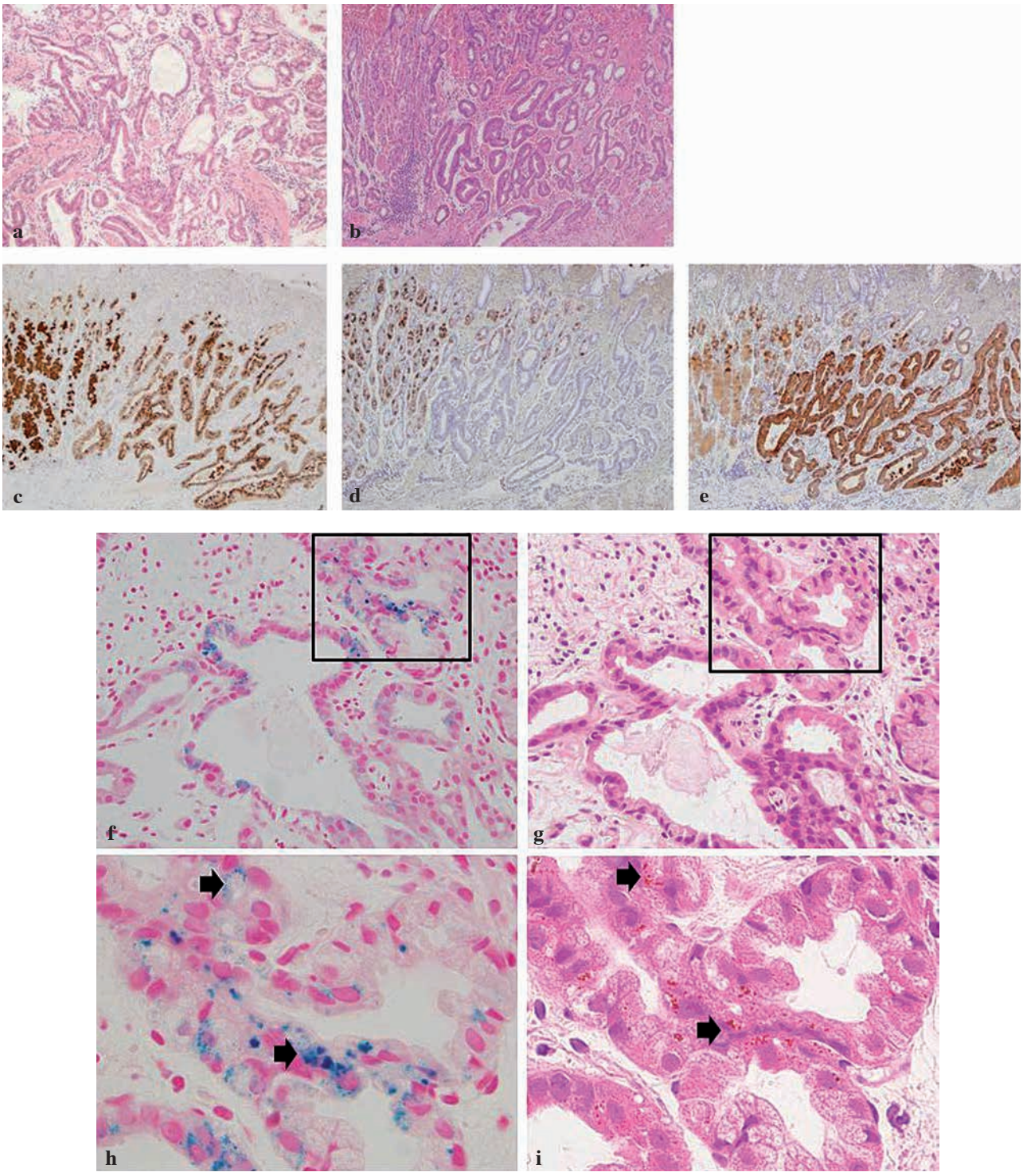

Fig. 2. — (a) Histological examination of the first conventional endoscopy revealed atypical glands suspected, but not diagnostic, of gastric adenocarcinoma of fundic gland type (GA-FD). (b) Histological findings of the endoscopic submucosal dissected specimen showed GA-FD mimicking fundic gland cells. Immunohistochemistry revealed that cancer cells were diffusely positive for (c) pepsinogen-I and (e) MUC6 and were partially positive for (d) H^+/K^+ ATPase. (f) Distinct Prussian blue (PB) staining was observed in the tumor cells at low magnification. (g) Hematoxylin and eosin (HE) sections under low magnification. It is difficult to find the hemosiderin-laden macrophages as brown granules in the corresponding area of adjacent sections stained positively with PB (h) Hemosiderin deposition was visualized more clearly by PB staining under high magnification (black arrows). (i) After HE staining, brown granules were visible in the corresponding area of consecutive sections stained distinctively with PB (black arrows). Magnified images of the areas outlined by black rectangles in f and g (40× magnification) correspond to h and i (1000× magnification), respectively.

Table 1. — **Endoscopic and clinicopathological features of previously reported cases**

Characteristics	Percentage and numbers
Age (years old)	66 (46-79)
Sex (male: female)	57:26
Tumor diameter (mm)	10.7 (3.0-42.0)
Form	
Protruding type	70.4% (38/54)
Flat type	7.4% (4/54)
Depressed type	22.2% (12/54)
Submucosal tumor shape	23.9% (9/38)
Color tone	
Whitish	59.2% (16/27)
Reddish	25.9% (7/27)
Brownish	14.8% (4/27)
Dilated vessels	18.1% (15/83)
Invasion depth	
M	31.3% (26/83)
SM	67.5% (56/83)
SS	1.2% (1/83)

M, mucosa ; SM, submucosa ; SS, subserosa.

With respect to the hemosiderin source, intratumoral hemorrhage may be related to dilated capillary proliferation, which is a characteristic endoscopic feature of this tumor. We thus speculate that the intratumoral hemorrhage resulted from capillary dilation, congestion, and rupture.

In conclusion, we described the case of a 66-year-old male patient with a flat-type GA-FD-CCP with black pigment dispersion and who underwent curative ESD. To our best knowledge, this is the first GA-FD-CCP report with distinctive black pigmentation caused by intratumoral hemorrhage. The black pigmentation was regarded as a key success factor for early diagnosis and endoscopic treatment.

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