Pathology International

Received: 6 May 2019 | Accepted: 13 July 2019

DOI: 10.1111/pin.12843

LETTER TO THE EDITOR

WILEY Pathology International

A case of multiple early gastric cancers with variant differentiation including gastric adenocarcinoma of fundic gland type

To the Editor

A new histological type of gastric neoplasia with chief cell differentiation was first reported as an unusual variant of fundic gland polyps.[1] Following the report of the first case of a gastric adenocarcinoma with chief cell differentiation in 2007,[2] the term gastric adenocarcinoma of fundic gland type (GA-FG) was proposed by Ueyama *et al.*[3] Since then authors have reported about this clinical entity and some details of GA-FG, such as morphologic appearance, pathogenesis, and genetic profiles, have been recently clarified.[4] In this report, we present a rare case of multiple early gastric cancers with variant differentiation including GA-FG.

An 80-year-old male was referred to our hospital for a detailed examination of the gastric tumor. In our hospital, a gastrointestinal fiberscope (GIF) was carried out and showed a Type 0-IIa (superficial elevated type) gastric tumor in the antrum. He was histologically diagnosed with gastric cancer and underwent endoscopic submucosal dissection (ESD). One year after ESD, GIF demonstrated two tumors located at the middle third of the stomach. Histological examination showed malignancy in each tumor; he was then admitted to our hospital for surgical intervention.

In his past-history, he had undergone endoscopic mucosal resection for a gastric tumor in another hospital 25 years before. He had not received medical treatment even though *Helicobacter pylori* was positive. He had also undergone hemicolectomy for colon cancer three years before.

Laboratory data in admission showed almost normal figures: WBC 4600/mm^3, RBC 479×10^4/mm^3, Hb 14.6 g/dL, Platelet 21.8×10^4/mm^3. Liver and renal function were within normal limit. Tumor markers of CEA and CA19-9 were at normal range. Abdominal enhanced CT showed neither distant metastasis nor lymph nodes swelling.

In GIF, the Type 0-IIa tumor at the anterior wall (Ant) of the antrum showed clear margin. The pathological finding of the excised tumor with ESD showed well-differentiated adenocarcinoma (tub1), 13×7 mm, T1a (M). Endoscopic curative treatment was performed. After one year from ESD, follow-up GIF showed two tumors. A Type 0-IIb (superficial flat type) tumor at the greater curvature (Gre) of the middle third of stomach was revealed without elevation or depression. The other tumor at Ant of the middle third of stomach exhibited a Type 0-I (protruding type) with polypoid like a submucosal tumor (Fig. 1a). According to the biopsy specimen, each histological diagnosis of the classification was malignancy. GIF was repeatedly carried out before operation, then the Type 0-I tumor at Ant could not endoscopically be clearly revealed.

Two tumors were diagnosed to be malignant and the surgical margin was unclear, thus he underwent total gastrectomy with regional lymphadenectomy and cholecystectomy. No lymph node metastasis was found, and curative operation was performed.

In macroscopic examination of excised stomach, the Type 0-IIb tumor at Gre was well recognized, yet the Type 0-I at Ant could not be detected (Fig. 1b). Sections of the resected stomach were totally made at 5 mm intervals and all specimens were carefully examined. The Type 0-IIb showed signet-ring cell carcinoma (sig), and clinicopathological diagnosis was 30×30 mm, T1a (M), pStage IA (Fig. 1b). The other tumor of Type 0-I was arising from the fundic gland, and it was diagnosed as gastric adenocarcinoma of fundic gland type (GA-FG). GA-FG occupied a very small restricted region with 3×3 mm in size, but it showed submucosal invasion as T1b(SM), pStage IA. Atypical cells with mildly enlarged nuclei were showed in the deep layer of the lamina propria mucosa. They mimic fundic gland cells, mainly chief cells and partially parietal cells (Fig. 1c). The immunohistochemical study showed positive staining of pepsinogen-I and MUC6 (Fig. 1d, e), but negative staining of H^+/K^+-ATPase and MUC5AC (Figures are not showed).

GA-FG was included in the pseudo-pyloric gland metaplasia (PGM), which diffusely expanded to the huge area from the middle to upper third of the stomach (Fig. 1b). Cytoplasm of PGM cells was stained weaker compared to that of GA-FG by H-E staining (Fig. 1f). Though nuclear atypia of the PGM cells was clarified, it was not enough evidence to elucidate a malignancy. In addition, chronic atrophic gastritis with intestinal metaplasia was observed in huge area of the antrum and epithelial cells of the mucosal layer were occupied with vacuolar.

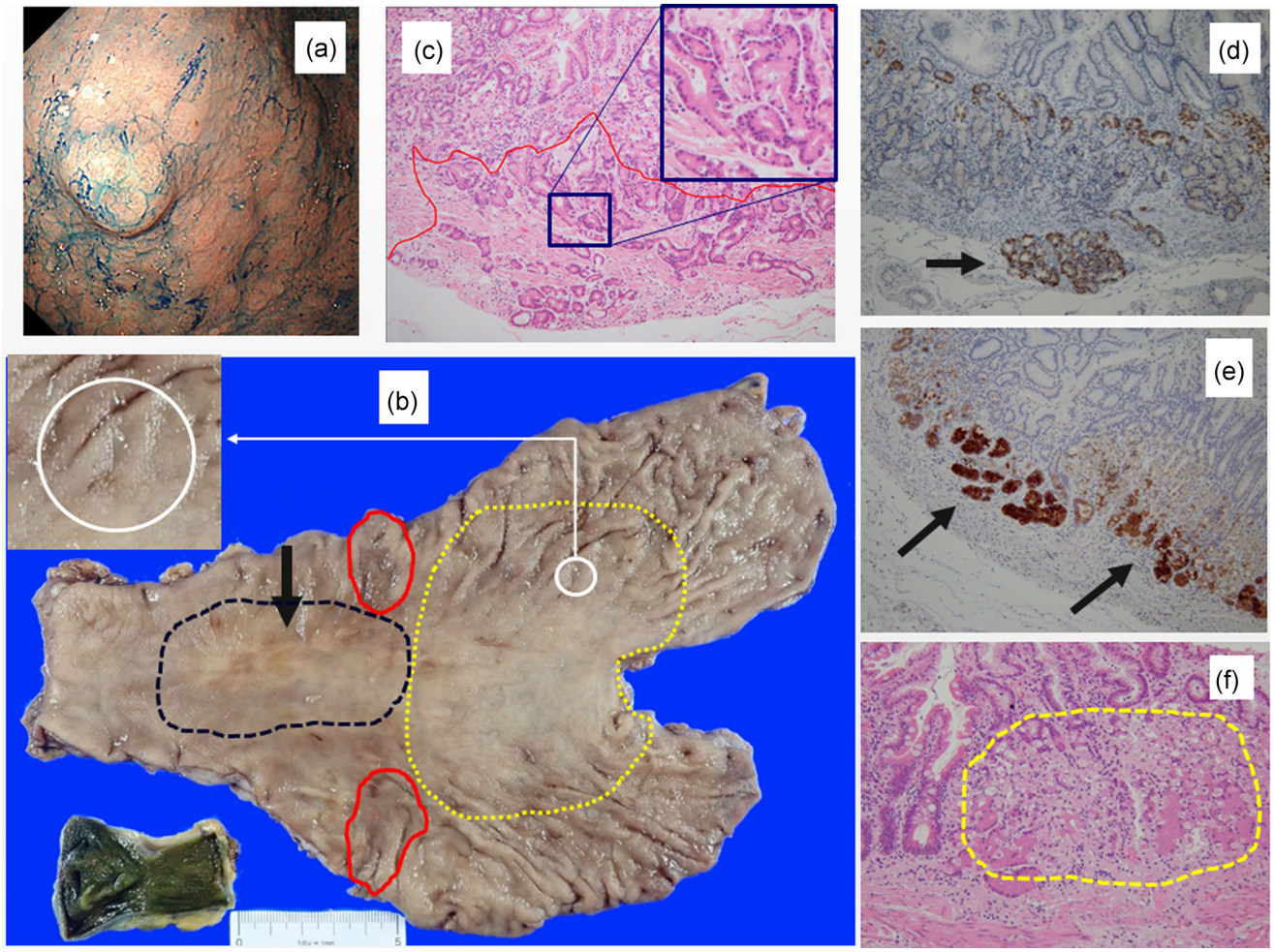

Figure 1 Histopathological and endoscopic findings. (**a**) Gastrointestinal fiberscope shows a Type 0-I (protruding type) tumor at the anterior wall of the middle third of the stomach with submucosal tumor-like shape. (**b**) A Type 0-IIb (superficial flat type) tumor 30 × 30 mm in size is showed (*red line*). A Type 0-I at the anterior wall is macroscopically not found. However, histological examination reveals a small region and shows gastric adenocarcinoma of fundic gland type (*white circle*). Pseudo-pyloric gland metaplasia expands huge area of middle to upper third of the stomach (*yellow line*). Intestinal metaplasia is showed at the antrum (*black line*), in which the endoscopic submucosal resection scar (*arrow*) is included. (**c**) H-E staining of gastric adenocarcinoma of fundic gland type. There are atypical cells with mildly enlarged nuclei in the deep layer of the lamina propria mucosa. They mimic fundic gland cells, mainly chief cells and partially parietal cells. Infiltration in the submucosal layer is showed (*red line*). (**d**) Immunohistochemical findings of gastric adenocarcinoma of fundic gland type. Positive staining of Pepsinogen-I (*arrow*). (**e**) Positive staining of MUC6 (*arrows*). (**f**) H-E staining of pseudo-pyloric gland metaplasia (PGM). Cells of PGM show nuclear atypia with weakly stained cytoplasm (*yellow line*).

Recently, GA-FG has been recognized as a rare subtype of gastric adenocarcinoma arising from the fundic gland. The incidence of GA-FG is rare and previously reported cases, especially from Asian countries, are about 50 in the English literature. Pathological analysis of GA-FG is characterized by a high frequency of submucosal invasion, rare occurrence of lymphatic and venous invasion, and low-grade malignancy.

Gastric glands are divided into two categories: the fundic gland is composed of mucous neck cell, chief cell and parietal cell, while the pyloric gland is composed of pyloric gland cell. According to immunohistochemical examination, the normal gland mucosa is expressed with four phenotypes: mucous neck cells express pepsinogen-I and MUC6; chief cells express pepsinogen-I; parietal cells express H^+/K^+-ATPase; and pyloric gland cells express MUC6. Chief cells lose the expression of MUC6, thus mucous neck cells are immunohistochemically regarded as a precursor of chief cells. Gastric neoplasia of fundic gland type is highly differentiated, thus the immunohistochemical profiles are most reliable for deciding the pyloric gland origin in neoplasia of the fundic gland cells.

The mechanism of carcinogenesis and formation in gastric cancer has been gradually elucidated. Chronic *H. pylori* infection leads eventually to chronic metaplasia and adenocarcinoma in the intestinal gland. In these days, different tumors arising from the stomach have been distinguished at the genomic level. Kushima *et al.*[4] studied the gene mutation of GA-FG and

showed the GNAS gene mutation in this clinical entity. The genetic aberrations that trigger carcinogenesis remain to be elucidated in the near future.

Recent authors have reported the following suggestions. Atrophic and metaplastic progression is extensive and severe in gastric adenoma patients. Patients with high-level atrophy and metaplasia are considered to show especially high risk of gastric cancer. Therefore, the larger the atrophic and metaplastic area is, the greater the cancer risk becomes. Pyloric gland adenoma is identified in a background of fundic gland mucosa with chronic active inflammation and pyloric metaplasia.[5] According to these studies and descriptions, we consider that GA-FG may progress from pyloric gland metaplasia to dysplasia, to adenoma and eventually, to adenocarcinoma. The accurate nomenclature could be further refined in the future when more cases are reported.

We reviewed our patient's histopathological studies. According to the whole gastric mapping, PGM expanded to the huge fundic gland of the stomach, and GA-FG was arising from the restricted small region in PGM. Our experience may suggest one of the cases where PGM is a precursor of GA-FG.

In conclusion, our patient had three early gastric cancers with variant differentiation of tub1, sig and GA-FG during a one-year period. We showed a rare case of GA-GF arising from pseudo-pyloric gland metaplasia using the whole mapping.

ACKNOWLEDGMENT

The authors would like to thank Professor Ryoji Kushima (Department Pathology, Shiga University School of Medicine) for pathological suggestions and advices.

DISCLOSURE STATEMENT

None declared.

AUTHOR CONTRIBUTIONS

MT and YMo designed this study and drafted the manuscript. YMi, MT, CYa and GU were the surgeons who operated on the patient. TM and YF were reviewing pathology slides and facilitating use of the photopathology. SE and CYu were the expert pathologists. All authors have read and approved the final manuscript.

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REFERENCES

1 Müller-Höcker J, Rellecke P. Chief cell proliferation of the gastric mucosa mimicking early gastric cancer: an unusual variant of fundic gland polyp. *Virchows Arch* 2003; **442**: 496–500.
2 Tsukamoto T, Yokoi T, Maruta S *et al.* Gastric adenocarcinoma with chief cell differentiation. *Pathol Int* 2007; **57**: 517–22.
3 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**: 609–19.
4 Kushima R, Sekine S, Matsubara A, Taniguchi H, Ikegami M, Tsuda H. Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. *Pathol Int* 2013; **63**: 318–25.
5 Kushima R, Matsubara A, Yoshinaga S *et al.* Clinicopathological characteristics of gastric-type adenoma (pyloric gland adenoma) - endoscopic findings, histogenesis, gene mutations, and malignant transformation. *Stomach and Intestine* 2014; **49**: 1838–49. (in Japanese).