DOI: 10.1111/pin.13254

LETTER TO THE EDITOR

Pathology International WILEY

Recurrence of gastric adenocarcinoma of fundic-gland mucosa type with black spots after endoscopic submucosal dissection and oral proton pump inhibitor discontinuation

To the Editor,

Hyperplastic and neoplastic lesions that differentiate into gastric fundic glands are generally either fundic gland polyps (FGP), oxyntic gland adenomas (OGA), or gastric adenocarcinomas of fundic-gland type (GA-FG). FGPs are hyperplastic lesions of the oxyntic mucosa. OGAs are benign epithelial neoplasms composed of columnar cells that differentiate into chief cells, parietal cells, or both. However, they have a high rate of progression to adenocarcinoma with submucosal invasion.[1] They involve gland ducts that histologically resemble fundic glands and cause lumen fusion and lateral gland dilatation. According to the World Health Organization (WHO) classification, if the tumor has invaded the submucosa, it is classified as GA-FG. However, in Japan, tumors are diagnosed as GA-FG if cellular and structural atypia are present, even if the lesion is intramucosal.[1] Gastric cancers are classified as gastric adenocarcinomas of fundic-gland mucosa type (GA-FGM) when they show differentiation into foveolar epithelium and fundic glands.[2]

We present an unusual case of a patient with GA-FGM. A 73-year-old man had a medical history of appendicitis, empyema, emphysema, and hypertension. Hematology tests showed no noteworthy abnormalities. He underwent *Helicobacter pylori* eradication for a gastric ulcer 17 years prior and was started on oral proton pump inhibitors (PPIs). PPI administration was continued, and the ulcer was monitored by performing annual upper gastrointestinal tract endoscopy.

Endoscopy showed a new type-0-IIa lesion, 25 mm in diameter, with black spots located in the posterior wall of the gastric corpus (Figure 1a). Narrow-band imaging showed a demarcation line from the perilesional mucosa. The microstructure of the mucosal surface was judged to be irregular, while the microvascular pattern was regular. Biopsy results suggested GA-FG. The lesion was resected by endoscopic submucosal dissection (ESD). ESD examination showed a type-0-IIa lesion, 2.5 × 2.2 cm, brown to gray in color, consisting of aggregated nodular protrusions (Figure 1b).

Histological examination showed a proliferative lesion in the fundic glands, with black material accumulated at various loci in the dilated gland ducts. In the proliferative fundic glands, there was irregular, budding-like branching found in various directions, with unusual cell arrangement, chief cells on the luminal sides of gland ducts, and parietal cells on the lateral sides (Figure 1c). The proliferative cells showed nuclear enlargement and disordered arrangement. The background gastric mucosa showed intestinal metaplasia and dilatation of the fundic glands. Immunohistochemistry findings of the fundic glands that showed irregular proliferation were positive for pepsinogen I in the chief cells, H+/K+ proton pump adenosine triphosphatase in some parietal cells, and mucin-6 (MUC6) mainly in the chief cells. There was also an admixture of MUC5AC-positive epithelial cells that showed foveolar epithelium differentiation. Ki-67-labeled cells were widely and irregularly distributed. The Ki-67 labeling index exceeded 10% where the Ki-67 positive cells were abundant.

The lesion was later reviewed and re-evaluated as GA-FGM; however, at the time of diagnosis of the ESD specimen, the epithelial atypia and disorganization could not be considered a neoplastic lesion, and clinically, the patient was on long-term PPI medication. Therefore, the patient was diagnosed with FGP associated with PPI administration. A part of this lesion was exposed in the horizontal margin.

After ESD, PPI administration was discontinued, and the patient's progression was monitored; however, 2 years later, gastroscopy showed recurrence of a similar,

This paper is based on a presentation at the 83rd Annual Meeting of the Japanese Society of Pathology, Chubu Division, in 2019. Its presenter, Akihiro Shioya, the first author of this paper, was given a Slide Conference Young Researchers' Award, Chubu Division of the Japanese Society of Pathology, for this presentation.

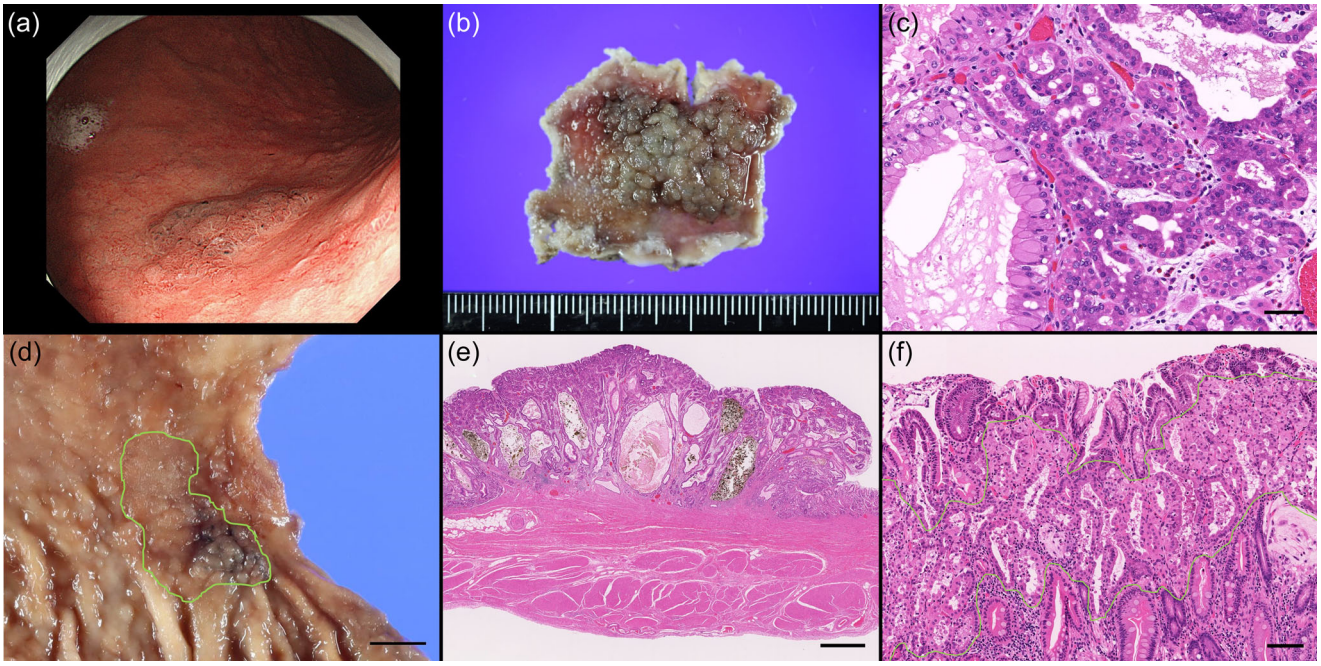

FIGURE 1 (a) Gastric endoscopy: A type-0-IIa lesion, 25 mm in diameter, with black spots, in the posterior wall of the gastric corpus. (b) Tissue obtained by endoscopic submucosal dissection of the posterior wall of the gastric corpus: A type-0-IIa lesion, 2.5 × 2.2 cm, brown to gray in color, consisting of aggregated nodular protrusions. (c) Hematoxylin-eosin-stained sample showing a fundic gland (chief cells, mucous neck cells, and parietal cells) with associated atypia, involving nuclear enlargement, disordered cell arrangement, and an admixture of MUC5AC positive foveolar epithelium-like cells (magnification ×200; scale bar: 50 μm). (d) Distal gastrectomy sample: visual observation of a protruding lesion (32 × 15 mm) in the posterior wall with the mucosal surface forming a coarse region at the unclear boundary on the lesser-curvature side (circled by green line). (e) A loupe image (prepared as a whole-slide image) of the protruding area showing submucosal scarring with irregular fundic gland proliferation similar to the one seen previously; black spots can be observed (scale bar: 1 mm). (f) In the coarsely textured mucosal surface, the atypical gastric fundic glands had proliferated laterally and destroyed the intestinal metaplastic gastric mucosa (circled by green line; magnification ×100; scale bar: 100 μm).

protruding lesion at the same locus. Even though the loci were considered nonlesional based on endoscopy, histological biopsy of the fundic glands showed architectural abnormalities. Since the lesion range was difficult to define, distal gastrectomy was performed. Post-ESD distal gastrectomy revealed that the scarred area had a protruding 32 × 15 mm lesion similar to that seen on ESD, with a mucosal surface, coarse texture, and unclear boundary to the lesser-curvature side (Figure 1d).

Histologically, the protruding area showing submucosal scarring also had irregular fundic gland proliferation with black spots (Figure 1e). In the area with coarsely textured mucosal surface, the atypical gastric fundic gland and mucosa-like cells that were positive for pepsinogen I, H+/K+ proton pump ATPase, or MUC5AC had proliferated laterally and destroyed the intestinal metaplastic gastric mucosa (Figure 1f). The fundic glands had a greater admixture and proliferation of fundic gland cells with mild nuclear enlargement and foveolar epithelium-like cells. The background gastric mucosa was dominated by areas of atrophic and hyperplastic change with intestinal metaplasia, but the remaining fundic glands showed no duct dilatation. Considering the lesions noted on ESD, the final diagnosis was changed to GA-FGM due to the progressive pattern, disordered cell arrangement, mucosal breakdown, and progression involving recurrence. The patient continued to be monitored 8 months postsurgery, and no recurrence has been found.

In recent studies, patients who were administered PPIs had larger FGPs and a higher FGP occurrence rate than those who were not, suggesting that long-term PPI administration increases the risk of FGPs.[3] Because our patient underwent oral PPI administration for 17 years and we underestimated the atypia of the proliferative zone, the gastric ESD lesion was initially diagnosed as FGP associated with PPI medication. However, despite discontinuation of PPI administration, post-ESD recurrence was found in the scar area, and the lesion developed a progressive pattern in a horizontal direction; hence, gastric neoplasia was considered a more appropriate diagnosis than a gastric hyperplastic lesion. In our patient, no submucosal invasion was found, but the lesion showed a progressive pattern outward from the protruding area, and a progression involving the breakdown of the intestinal metaplastic mucosa (Figure 1f).

Therefore, although the lesion was intramucosal, it was diagnosed as cancer based on the Japanese concept of cancer.

The recurrence of GA-FG and OGA is uncommon, as demonstrated in Iwamuro et al.'s study, in which only two patients of 113 showed recurrence.[4] This neoplasia recurrence had an unusual progression; thus, appropriate distance from the resection stump and careful follow-up of the patient should be ensured.

A unique characteristic of this lesion was that many black spots were endoscopically and histologically noticeable in the dilated gland ducts of the tumor. It should be noted that lesions that have black spots are often non-neoplastic lesions, but they may also occur in cases of gastric cancer.[5]

We diagnosed FGP based on ESD; however, after subsequent recurrence the gastrectomy sample was reassessed, and the diagnosis was changed to GA-FGM with black spots, constituting a highly unusual case.

AUTHOR CONTRIBUTIONS

Akihiro Shioya, Shintaro Terahata, Takahiko Nakajima, Toshiko Kakiuchi, Motona Kumagai, Jia Han, and Sohsuke Yamad reviewed the clinical information, patient follow-up, and the histology reports. Akihiro Shioya wrote the manuscript, and all authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

We are grateful to Dr. Ryoji Kushima (Division of Diagnostic Pathology, Shiga University of Medical Science Hospital) for assisting the pathological diagnosis. We would also like to thank Editage (www.editage.com) for English language editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

This case study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee of Tonami General Hospital (No. 2021042).

Akihiro Shioya[1,2]
Shintaro Terahata[2]
Takahiko Nakajima[2]
Toshiko Kakiuchi[2]
Motona Kumagai[3]
Jia Han[1]
Sohsuke Yamada[1]

[1]*Department of Pathology and Laboratory Medicine, Kanazawa Medical University, Kahoku, Ishikawa, Japan*
[2]*Department of Diagnostic Pathology, Tonami General Hospital, Tonami City, Toyama, Japan*
[3]*Department of Pathophysiological and Experimental Pathology, Kanazawa Medical University, Kahoku, Ishikawa, Japan*

ORCID

Akihiro Shioya https://orcid.org/0000-0002-1863-5368
Sohsuke Yamada http://orcid.org/0000-0003-2662-0024

REFERENCES

1. Genta RMG, Yao T, Vieth M, Carneiro F, Fukayama M, Grabsch HI, et al. WHO classification of tumours. In: Lokuhetty D, White VA, Watanabe R, Cree LA, editors. *Digestive system tumours*. 5th ed. Lyon Cedex, France: World Health Organization; 2019. p. 67–92.
2. Ueyama H, Yao T, Akazawa Y, Hayashi T, Kurahara K, Oshiro, et al. Gastric epithelial neoplasm of fundic-gland mucosa lineage: proposal for a new classification in association with gastric adenocarcinoma of fundic-gland type. J Gastroenterol. 2021;56:814–28.
3. Fukuda M, Ishigaki H, Sugimoto M, Mukaisho K-I, Matsubara A, Ishida, et al. Histological analysis of fundic gland polyps secondary to PPI therapy. Histopathology. 2019;75:537–45.
4. Iwamuro M, Kusumoto C, Nakagawa M, Kobayashi S, Yoshioka M, Inaba, et al. Endoscopic resection is a suitable initial treatment strategy for oxyntic gland adenoma or gastric adenocarcinoma of the fundic gland type. Sci Rep. 2021;11:7375.
5. Sato Y, Fujino T, Kasagawa A, Morita R, Ozawa SI, Matsuo, et al. Twelve-year natural history of a gastric adenocarcinoma of fundic gland type. Clin J Gastroenterol. 2016;9:345–51.