Endoscopic Findings and Treatment of Gastric Neoplasms in Familial Adenomatous Polyposis

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ABSTRACT

Purpose: Gastric neoplasia is a common manifestation of familial adenomatous polyposis (FAP). This study aimed to elucidate the clinical characteristics, endoscopic features including fundic gland polyposis (FGPsis), and treatment outcomes of gastric neoplasms (GNs) in patients with FAP.

Materials and Methods: A total of 35 patients diagnosed with FAP, including nine patients from four pedigrees who underwent esophagogastroduodenoscopy (EGD), were investigated regarding patient characteristics, GN morphology, and treatment outcomes.

Results: Twenty-one patients (60.0%) had 38 GNs; 33 (86.8%) and 5 (13.2%) were histologically diagnosed with adenocarcinoma and adenoma, respectively. There were no specific patient characteristics related to GNs. Nodule-type GNs were more prevalent in patients with FGP than without (52.2% vs. 0.0%, P=0.002) in the upper body of the stomach. Conversely, depressed-type GNs were fewer in patients with FGPsis than in those without (13.0% vs. 73.3%, P<0.001). Slightly elevated-type GNs were observed in both groups (34.8% vs. 20.0%, P=0.538). Within pedigrees, the background gastric mucosa and types of GNs varied. In total, 24 GNs were treated with endoscopic submucosal dissection (ESD) and eight with endoscopic mucosal resection (EMR). EMR was selected for GNs with FGPsis because of the technical difficulty of ESD, resulting in a lower en bloc resection rate (62.5% vs. 100%, P=0.014).

Conclusions: Our study indicates the necessity of routine EGD surveillance in patients diagnosed with FAP. Notably, the morphology and location of GNs differed between patients with and without FGPsis. Endoscopic treatment and outcomes require more attention in cases of FGPsis.

Keywords: Gastric neoplasms; Endoscopic submucosal dissections; Endoscopic mucosal resections; Familial adenomatous polyposis
INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary neoplastic disease caused by a mutation in the adenomatous polyposis coli (APC) gene and is characterized by the presence of hundreds to thousands of adenomas in the rectum and colon [1,2]. Patients with FAP develop colorectal cancer before their 60s, unless a prophylactic colectomy is performed [1,3,4]. They also develop various extracolonic manifestations such as duodenal and gastric neoplasms (GNs), including gastric cancer (GC) and gastric adenoma (GAD), a precursor of GC in patients with FAP [5]. Especially in Asian countries including Japan, an increased risk of GC has been reported in patients with FAP [6-10]. GC accounts for 2.8% of deaths in patients with FAP in Japan, second to 5.6% of deaths due to duodenal cancer among extracolonic gastrointestinal manifestations [10]. However, the clinical risk factors for GNs in patients with FAP remain to be fully understood, except for an *Helicobacter pylori* infection [8].

In esophagogastroduodenoscopy (EGD) surveillance, the background mucosa should be monitored, as the risk of GNs can change depending on their status. Fundic gland polyps (FGPs) are the most common finding in patients with FAP (64%–88%) [11-13]. FGPs in patients with FAP frequently exhibit somatic mutations in the APC gene and often form fundic gland polyposis (FGPsis), polypoid mound, and carpeting (Fig. 1), which are considered risk factors for GNs [11,14-18]. Moreover, atrophic gastritis due to *H. pylori* infection is associated with an increased risk of GNs in patients with FAP [8,16]. Therefore, GNs can be detected more efficiently based on the findings of the background mucosa during EGD surveillance. Among these findings, FGPsis has a high prevalence of 49% [11]. However, macroscopic findings of GNs based on background mucosa, particularly FGPsis, have not been thoroughly investigated and are necessary for early detection. Furthermore, it remains unknown whether endoscopic findings regarding background mucosa and macroscopic GN types are similar within pedigrees. Such information will be useful for predicting the future risks of GNs and help detect GNs.

Among the treatment options for GNs, endoscopic treatment, such as endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), is minimally invasive and efficient for GNs in patients with FAP [5,11]. However, because of the rarity of GN cases with FAP, further research regarding its procedural outcomes and clinical course is warranted.

Therefore, we aimed to elucidate the clinical and endoscopic features of GNs by focusing on FGPsis. Furthermore, we compared the endoscopic findings within the same pedigrees. We also investigated the endoscopic treatment outcomes for GNs in patients with FAP.

![Fig. 1. Representative endoscopic images of fundic gland polyposis, carpeting, and polypoid mound. (A) Fundic gland polyposis: a stomach with over 100 fundic gland polyps. (B) Carpeting: the fundus and proximal body of the stomach covered in polyps without any intervening visible normal mucosa. (C) Polypoid mound: one large polyp or a collection of polyps over 2 cm in carpeting.](https://jgc-online.org)
MATERIALS AND METHODS

Study subjects
We identified 35 patients with FAP who underwent EGD at least once at the Niigata University Hospital between August 1994 and September 2021. FAP was diagnosed in cases with >100 colorectal polyps or a positive family history of FAP with <100 colorectal polyps [19]. Nine of the 35 patients were from four different pedigrees. We assessed the patients’ characteristics, EGD findings, treatment outcomes, and clinical courses. The results were compared between patients with and without GNs or those with and without FGPs. We also compared the EGD findings of patients from the same pedigree.

Patient characteristics included sex, age, family history of FAP, follow-up period, and malignant tumors in other regions of the gastrointestinal tract. The follow-up period was defined as the period between the first and last day of EGD. We performed annual endoscopic surveillance of patients without GNs. Once patients were diagnosed with GNs, endoscopic surveillance was scheduled every 6 months after GN treatment. A previous report suggested that the long-term use of proton pump inhibitors induces FGPs in the stomach [20]. Therefore, we investigated the use of acid secretion inhibitors. This study was performed in accordance with the Declaration of Helsinki and the use of opt-out consent was approved by the ethical committee of Niigata University (approval number: 2021-0138).

EGD evaluation
Endoscopic findings of FGPs, carpeting, polypoid mound, and atrophic gastritis were analyzed between the first and last EGD. We also investigated the prevalence of GNs, including GC and GAD, diagnosed through biopsies or resected specimens according to the Japanese classification of gastric carcinoma [21]. GC in this classification is almost equivalent to non-invasive high-grade dysplasia/neoplasia, non-invasive carcinoma, and invasive carcinoma, according to the WHO [22,23]. GAD includes low-grade dysplasia/neoplasia [22,23]. The tumor size, location, macroscopic type, and color were also evaluated.

FGPs was defined as a state with >100 FGPs in the stomach [14] and carpeting as the fundus and proximal body of the stomach covered with polyps without any intervening visible normal mucosa [14]. A large poly or a collection of polyps >2 cm in the carpeting was defined as a polypoid mound [14]. The presence and extent of atrophic gastritis was determined according to the Kimura–Takemoto classification [24]. Nodule-type GN was defined as a nodule-like lesion with a tumor height >3 mm, depressed-type GN as a macroscopically depressed lesion, and slightly elevated-type as a flat elevated lesion with a tumor height <3 mm. When the GNs were approximately 3 mm, we used biopsy forceps to measure the tumor size. Representative endoscopic images and histopathology of nodule-type, depressed-type, and slightly elevated-type GNs are shown in Fig. 2. If several GNs were found during the same EGD session, they were declared simultaneous GNs. If GNs were found during different EGD sessions, they were declared metachronous GNs. When metachronous GNs were detected, we checked previous EGD images. If GNs had already existed in the previous EGD images, these lesions were excluded from the metachronous GN group and declared missed GNs.

Endoscopic treatment
ESD or EMR was performed for GC confined to the mucosa or slightly invading the submucosa on EGD, with no apparent metastasis on computed tomography, based on the Japanese GC treatment guidelines [25]. For GADs diagnosed by biopsy, ESD or EMR was
performed when the lesions were endoscopically suspected to be an adenocarcinoma, and the invasion depth was suspected to be intramucosal. Intramucosal invasion was confirmed if none of the following endoscopic findings existed: irregular surface, including nodules in the depressed area; submucosal tumor-like elevation without flexibility; abnormal converging folds such as clubbing and fusion; and deep ulceration with marked marginal elevation [26]. We retrospectively evaluated the treatment outcomes, including procedure time, en bloc resection rates, complications, and clinical course. The pathological results, including tumor size, invasion depth, tumor involvement in lateral and vertical margins, and lymphovascular involvement, were also evaluated.

**Statistical analysis**

Categorical variables are presented as numbers and percentages, and continuous variables as medians and ranges. The χ² test was used for categorical variables, and the Mann–Whitney U test for continuous variables. A P-value <0.05 denoted statistical significance in all analyses. EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for statistical analysis [27].

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**Fig. 2.** Representative endoscopic images of GNs. (A) A nodule-type GN in the upper body of the stomach in patients with FGPsis. (B) Histopathological image of the nodule-type GN in a low-power field. Foveolar-type gastric adenocarcinoma can be seen on the pyloric gland adenoma. (C) Magnified image of the area surrounded by a green rectangle. Dense irregular papillary glands can be observed in the adenocarcinoma. (D) A depressed-type GN is frequently seen in the lower body of the stomach in patients without FGPsis. (E) Histopathological image of the depressed-type GN in a low-power field. (F) Magnified image of the area surrounded by a red rectangle. Dense irregular glands and increased nuclear density can be seen in the tumor. Furthermore, a proliferative zone can be observed in the shallow mucosa. This case was diagnosed as a well-differentiated adenocarcinoma. (G) A slightly elevated-type GN is seen in both groups. (H) Histopathological image of the slightly elevated-type GN in a low-power field. Dense dysplastic glands with nuclear pseudostratification can be seen. This case was diagnosed as a well-to-moderately differentiated adenocarcinoma. (I) Magnified image of the area surrounded by a yellow rectangle. Fundic glands and dilated foveolar glands can be seen in the deep layer of the mucosa. GN = gastric neoplasm; FGPsis = fundic gland polyposis.
RESULTS

In total, 35 patients with FAP were included in this study. The median age (range) of the patients was 32 (13.0–70.0) years. Twenty-two (62.9%) patients had FGPsis and 21 (60%) had GNs during the 115-month follow-up period (Table 1). The median (range) follow-up period did not differ significantly among patients with and without GNs (148.0 [9.0–322.0] vs. 94.5 [0.0–275.0] months, P=0.061). Female sex (57.1% vs. 35.7%, P=0.369) and familial history of FAP (52.4% vs. 28.6%, P=0.296) were more prevalent among patients with GNs, but the differences were not significant. Endoscopic findings of atrophic gastritis (33.3% vs. 35.7%, P=1.000), FGPsis (57.1% vs. 71.4%; P=0.617), carpeting (28.6% vs. 14.3%, P=0.565), and polypoid mounds (9.5% vs. 7.1%, P=1.000) did not differ with the GN status. Proton pump inhibitor use (9.5% vs. 7.1%, P=1.000), H2 antagonist use (0.0% vs. 14.3%, P=0.298), and malignant tumors in other regions of the gastrointestinal tract did not differ between the groups.

EGD findings characteristics in patients with GNs

We detected 38 GNs in 12 patients with FGPsis and nine patients without: 33 adenocarcinomas and five adenomas. GNs were classified according to the presence of FGPsis (Table 2). The frequency of atrophic gastritis tended to be lower in patients with FGPsis than in those without, but this was not statistically significant (16.7% vs. 55.6%, P=0.161). The frequencies of metachronous GN (16.7% vs. 22.2%, P=1.000) and simultaneous GN (25.0% vs. 22.2%, P=1.000) were not significantly different between the 2 groups. Two cases of missed GN were detected in the non-FGPsis group (16.7% vs. 0.0%, P=0.486). The nodule type was significantly more frequent in GNs with FGPsis (52.2% vs. 0.0%, P=0.002), whereas the depressed type was more frequent in GNs without FGPsis (13.0% vs. 73.3%, P<0.001). The frequency of the slightly elevated type was not significantly different between the 2 groups (34.8% vs. 20.0%, P=0.538). The dominant color was red in both the nodule (41.7%) and depressed (64.3%) types, and white in the slightly elevated type (63.6%). The histopathological results showed that the rates of GC in the nodule, depressed, and slightly elevated types were 91.7%, 76.9%, and 90.0%, respectively (P=0.868), indicating no significant difference.

Table 1. Patients’ characteristics of FAP with and without GN

| Characteristics               | Total (n=35) | Patients with GN (n=21) | Patients without GN (n=14) | P-value*  |
|------------------------------|-------------|-------------------------|---------------------------|-----------|
| Age of initial EGD (yr)      | 32.0 (13.0–70.0) | 32.0 (14.0–70.0) | 32.0 (13.0–66.0) | 0.946     |
| Sex, female                  | 17 (48.6)  | 12 (57.1)               | 5 (35.7)                  | 0.369     |
| Familial history of FAP      | 15 (42.9)  | 11 (52.4)               | 4 (28.6)                  | 0.298     |
| Follow-up period (mon)       | 115.0 (0.0–322.0) | 148.0 (9.0–322.0) | 94.5 (0.0–275.0) | 0.061     |
| Proton pump inhibitor use    | 2 (5.7)    | 0 (0.0)                 | 2 (14.3)                  | 0.298     |
| Atrophic gastritis           | 12 (34.3)  | 7 (33.3)                | 5 (35.7)                  | 1.000     |
| Fundic gland polyposis       | 22 (62.9)  | 12 (57.1)               | 10 (71.4)                 | 0.617     |
| Carpeting                    | 8 (22.8)   | 6 (28.6)                | 2 (14.3)                  | 0.565     |
| Polypoid mound               | 3 (8.5)    | 2 (9.5)                 | 1 (7.1)                   | 1.000     |
| Malignant tumors in other GI |             |                         |                           |           |
| Colon                        | 5 (14.3)   | 4 (19.0)                | 1 (7.1)                   | 0.622     |
| Rectum                       | 2 (5.7)    | 1 (4.8)                 | 1 (7.1)                   | 1.000     |
| Duodenum                     | 6 (17.1)   | 4 (19.0)                | 2 (14.3)                  | 1.000     |
| Deaths                       | 2 (5.7)    | 1 (4.8)                 | 1 (7.1)                   | 1.000     |
| Deaths due to GN             | 1 (2.9)    | 1 (4.8)                 | 0 (0.0)                   | 1.000     |

Categorical variables are presented as numbers (%), and continuous variables as medians (ranges).

GN = gastric neoplasm; EGD = esophagogastroduodenoscopy; FAP = familial adenomatous polyposis; GI = gastrointestinal.

*Statistical analysis between patients with GN and patients without GN.

A total of 33 adenocarcinomas were detected in 17 patients, and five adenomas were detected in five patients (one patient had both adenocarcinoma and adenoma).
GNs with FGPsis were more frequent in the upper body (69.6% vs. 13.3%, P=0.002), whereas GNs without FGPsis were more frequent in the lower body of the stomach (73.3% vs. 21.7%, P=0.005).

Comparison of endoscopic findings among 9 patients from 4 pedigrees
Among all pedigrees, patients without atrophic gastritis had FGPsis, while those with atrophic gastritis did not, indicating that the background stomach mucosa could vary among the same pedigrees, depending on *H. pylori* infection (Table 3). In pedigree 3, the endoscopic findings of the background mucosa and GNs differed between the mother and daughter.

Table 3. Differences in the endoscopic findings among patients in the same pedigree

| Variables          | Pedigree 1 | Pedigree 2 | Pedigree 3 | Pedigree 4 |
|--------------------|------------|------------|------------|------------|
|                    | Age (years) | FGPsis     | AG         | GN         | Type of GN   |
| Brother            | 37         | (-)        | (-)        | (-)        | Depressed    |
| Brother            | 35         | (-)        | (-)        | (-)        |              |
| Father             | 58         | (-)        | (+)        | (+)        | Depressed    |
| Daughter           | 30         | (-)        | (-)        | (-)        |              |
| Mother             | 60         | (-)        | (+)        | (+)        | Depressed    |
| Son                | 33         | (-)        | (-)        | (-)        | Slightly elevated |
| Daughter           | 37         | (+)        | (-)        | (+)        |              |
| Mother             | 81         | (-)        | (+)        | (-)        | Nodule       |
| Daughter           | 51         | (-)        | (-)        | (+)        |              |

FGPsis = fundic gland polyposis; GN = gastric neoplasm; AG = atrophic gastritis.
Outcomes of endoscopic treatment

Of the 38 GNs, 32 (ESD, n=24; EMR, n=8) were treated endoscopically. One GN was treated surgically because it had spread from the lower to the upper body of the stomach, rendering it too large for endoscopic resection. The remaining 5 GNs were followed without treatment. Three of them were low-grade adenomas; 2 of them were adenocarcinomas, but constituted small lesions, and their endoscopic findings remained unaltered for several years. All resected lesions were histologically intramucosal GNs. There were no cases with positive vertical resection margins or lymphovascular involvement. The frequency of nodule-type GNs was significantly lower in the ESD group than in the EMR group (25.0% vs. 75.0%, P=0.030), and the frequencies of the slightly elevated type (37.5% vs. 0.0%, P=0.070), flat type (4.2% vs. 0.0%, P=1.000), and depressed type (33.3% vs. 25.0%, P=0.036) did not differ significantly, nor did the tumor size, color, and location. The en bloc (100.0% vs. 62.5%, P=0.014) and negative lateral resection margin (91.7% vs. 50.0%, P=0.036) rates were higher in the ESD group. Patients with positive lateral resection margins were followed without additional therapy, but there were no recurrent cases, except for the case we later present in this section. The procedure time was longer in the ESD group (110.0 vs. 24.0 minutes, P=0.038). The complication rates were similar (12.5% vs. 12.5%, P=1.000), and there were no life-threatening complications in either group (Table 4).

Endoscopic treatment outcomes of GNs with and without FGPsis were analyzed. No statistically significant differences were observed in the rate of en bloc resection (85.7% vs. 100.0%, P=0.498), negative lateral resection margin (76.2% vs. 90.9%, P=0.592), procedure time (110.0 vs. 85.0 minutes, P=0.585), tumor size (29.5 vs. 32.0 mm, P=0.763), perforation rate (14.3% vs. 0.0%, P=0.498), and bleeding (4.8% vs. 0.0%, P=1.000) (Table 5). Two patients died during the study period: one due to GC and the other due to an unrelated cause. Residual GC rapidly progressed after EMR with a positive lateral resection margin in one patient with GC in the FGPsis.

Table 4. Procedure outcomes and clinical courses of endoscopic treatment for GNs

| Variables                        | Total (n=32) | ESD (n=24) | EMR (n=8) | P-value* |
|----------------------------------|-------------|------------|-----------|----------|
| Macroscopic type                 |             |            |           |          |
| Nodule                           | 12 (37.5)   | 6 (25.0)   | 6 (75.0)  | 0.030    |
| Slightly elevated                | 9 (28.1)    | 9 (37.5)   | 0 (0.0)   | 0.070    |
| Flat                             | 1 (3.1)     | 1 (4.2)    | 0 (0.0)   | 1.000    |
| Depressed                        | 10 (31.3)   | 8 (33.3)   | 2 (25.0)  | 1.000    |
| Tumor size (mm)                  | 30.0 (5.0–62.0) | 30.0 (16.0–62.0) | 30.0 (5.0–40.0) | 0.699 |
| Location, upper                  | 18 (56.3)   | 12 (50.0)  | 6 (75.0)  | 0.411    |
| En bloc resection                | 29 (90.6)   | 24 (100.0) | 5 (62.5)  | 0.014    |
| Procedure time (min)             | 90.0 (16.0–310.0) | 110.0 (47.0–310.0) | 24.0 (16.0–90.0) | 0.038 |
| Adenocarcinoma                   | 29 (90.6)   | 22 (91.7)  | 7 (87.5)  | 1.000    |
| Invasion depth (m)†              | 32 (100.0)  | 24 (100.0) | 8 (100.0) | 1.000    |
| Lymphovascular involvement       | 0 (0.0)     | 0 (0.0)    | 0 (0.0)   | 1.000    |
| Negative lateral resection margin| 26 (81.3)   | 22 (91.7)  | 4 (50.0)  | 0.036    |
| Negative vertical resection margin| 32 (100.0) | 24 (100.0) | 8 (100.0) | 1.000    |
| Complications                    | 4 (12.5)    | 3 (12.5)   | 1 (12.5)  | 1.000    |
| Perforation                      | 3 (9.3)     | 3 (12.5)   | 0 (0.0)   | 0.726    |
| Bleeding                         | 1 (3.1)     | 0 (0.0)    | 1 (12.5)  | 0.557    |
| Local recurrence                 | 1 (3.1)     | 0 (0.0)    | 1 (12.5)  | 0.557    |
| Metastasis                       | 1 (3.1)     | 0 (0.0)    | 1 (12.5)  | 0.557    |
| Deaths                           | 1 (3.1)     | 0 (0.0)    | 1 (12.5)  | 0.557    |

Categorical variables are presented as numbers (%), and continuous variables as medians (ranges). GN = gastric neoplasm; ESD = endoscopic submucosal dissection; EMR = endoscopic mucosal resection.

*Statistical analysis between the ESD and EMR groups. †Lesions confined within the mucosal layer.
A 36-year-old female diagnosed with FAP underwent surveillance EGD and total colectomy for transverse colon cancer at 31 years of age. Surveillance EGD showed a reddish nodule-type lesion in the upper body of the stomach, which was diagnosed as adenocarcinoma (Fig. 3A). The invasion depth of the lesion was endoscopically considered to be intramucosal, and the tumor was resected. With a tumor size ≤2 cm, both EMR and ESD were indicated [25]. The lesion was located in the fornix of the stomach, where ESD is technically challenging; therefore, EMR was performed. However, snaring of the lesion was difficult because of the numerous small polyps surrounding it, resulting in piecemeal resection. In the final histological evaluation, the resected lesion was diagnosed as a well-differentiated adenocarcinoma confined to the mucosa, but the lateral resection margin was positive (Fig. 3B). We recommended additional surgery because the presence of a residual GC was strongly suspected. The patient preferred a close EGD follow-up because of the invasiveness of total gastrectomy after total colectomy, to which we agreed. Subsequently, a reddish elevated lesion with a central depression developed on the oral side of the EMR scar 2 months after EMR (Fig. 3C). The biopsy specimen from the lesion showed a well-differentiated adenocarcinoma, indicative of a rapidly progressing GC. Computed tomography after EGD revealed liver metastasis (Fig. 3D). Despite intensive treatment including chemotherapy, the tumor progressed and the patient died 18 months after EMR.

**DISCUSSION**

In this study, 60% of the patients with FAP had GNs on EGD surveillance during an approximately 10-year follow-up period, with no specific characteristics related to GNs. We demonstrated that nodule-type GNs were predominant in the upper body of the stomach in patients with FGPsis, whereas depressed-type GNs were common in the lower body of patients without FGPsis. Endoscopic findings of the background mucosa and GN types varied, even within the same pedigrees, depending on the presence of atrophic gastritis.
Selection of EMR or ESD was based on FAP-specific parameters, such as FGPsis and tumor size, and EMR was conducted for GNs considered to be technically challenging for ESDs. Our study is consistent with previous reports regarding the high prevalence of GNs without any significant risk factors [6-10], suggesting that EGD surveillance is required for all patients with FAP. Recent guidelines recommend a 3- to 6-month interval surveillance for EGD [28] for all cases diagnosed with FAP. Surveillance EGD is recommended to begin between 25 and 30 years of age [28,29]. However, the median age (range) of the patients with GNs was 32 (14–70) years in this study, and 1 pediatric patient was included. Whether EGD surveillance is appropriate for pediatric patients requires further research.

Previous studies reported that elevated lesions in the middle to upper body of the stomach and depressed lesions in the lower body were characteristics of GNs in patients with FAP [8,11,30]. We further found that the former type of GN often developed in patients with FGPsis and the latter in patients without. FGP with dysplasia is observed in 25%–41% of patients with FAP, and a large polyp size (>1 cm) is associated with FGP dysplasia [12,31]. Furthermore, pyloric gland adenoma, which develops in the fundic gland area, is observed in 6% of patients with FAP [32,33]. Pyloric gland adenoma has malignant potential in the general population [34], and we observed a case of adenocarcinoma alongside pyloric gland adenoma, which likely led to nodule-type GN (Fig. 2A-C). Therefore, nodule-type

Fig. 3. GC recurrence after EMR.
(A) A reddish nodule-type lesion (white arrow) in the upper body of the stomach, resected by EMR. (B) A well-differentiated adenocarcinoma with a positive lateral resection margin. (C) A reddish flat-elevated lesion with a central depression on the oral side of the EMR. (D) The biopsy specimen from the lesion shows a well-differentiated adenocarcinoma. Computed tomography image showing liver metastasis. (A, B) The white circle and triangle compare the endoscopic images before and after the detection of advanced GC. GC = gastric cancer; EMR = endoscopic mucosal resection.
GNs may be derived from FGPs or pyloric gland adenomas. A slightly elevated lesion is also a characteristic of GNs in the middle to upper body of the stomach in patients with FAP [30,35]. Such lesions were frequently observed in both groups. Therefore, it is important to identify this type independently of the FGPs. Its development in the carpeting renders macroscopically distinguishing a lesion from FGPs challenging. Notably, there were 2 missed cases among the slightly elevated type GNs. The elevated type was predominantly white (63.6%), which may assist in detecting this type of GN among FGPs [35]. Our study demonstrated that the macroscopic types and locations of GNs varied depending on the presence of FGPs. These findings are expected to make surveillance EGD more efficient.

Our study showed that patients, even within the same pedigree, could show different endoscopic characteristics. Considering the high prevalence of GNs among patients with FAP in this study, it is likely that germine mutations affect the development of GNs. In addition, a previous study showed that different somatic KRAS mutations were found in different GNs in a single patient with FAP [36]. Furthermore, different patients from the same pedigree with APC germine mutations showed different phenotypes of background mucosa and macroscopic types of GC depending on H. pylori infection status [18]. These results imply that somatic mutations and epigenetic alterations might also affect the stomach background mucosa and development of GNs [16,18,36,37].

There is no consensus on the indication for endoscopic resection of GNs in FAP [29,38,39]. However, minimally invasive treatment is favorable as a history of abdominal surgery is a risk factor for desmoid tumors in patients with FAP [40]. Furthermore, gastrectomy can burden patients with FAP who have undergone prophylactic colectomy. Therefore, endoscopic resection remains an option because it can preserve the stomach, bears fewer complications, and affords low recurrence rates for GNs in patients with FAP [15]. In this study, ESD was superior to EMR in terms of the en bloc resection and negative resection margin rates but resulted in increased complications and prolonged procedure time. Although the clinical outcome was favorable in the cases treated with ESD, the en bloc resection rate was only 62.5% in the EMR group, which led to a low negative resection margin rate (50.0%). EMR is technically easier than ESD and is an adequate treatment for the small-nodule type GNs. Hence, EMR was mostly performed for such GNs in the upper body of the stomach. However, GNs often develop among numerous polyps in patients with FAP. In such a condition, complete resection of GNs by EMR is difficult. Therefore, as with GC in the general population [41,42], ESD is the first choice for intramucosal GNs in patients with FAP, despite requiring significant endoscopic skills. Although there were no statistically significant differences due to the small sample size, our study showed the tendencies of lower en bloc resection rate, higher complication rate, and longer procedure time in GNs with FGPs than in those without. Therefore, for lesions developed among FGPs, technical ingenuity, such as the use of the countertraction method, will be necessary [43,44].

We experienced progression of GC after incomplete EMR, leading to the patient's death. Difficulty in diagnosing the tumor margin might have been the reason for the incomplete resection. We retrospectively observed a slightly elevated whitish lesion surrounding the nodular lesion (Fig. 3A). Such a whitish area might have been a GC, accounting for the positive lateral resection margin on EMR. This case highlights the difficulty in diagnosing the range of GNs, especially when slightly elevated lesions develop in patients with FGPs. This also underscores the importance of identifying the endoscopic characteristics of GNs using white-light imaging for the correct diagnosis of the tumor margin.
Furthermore, we reviewed the endoscopic images taken when EMR was performed and investigated the location where advanced GC occurred (Fig. 3A and C). However, we found no signs of GC when EMR was performed, indicating rapid progression of the lesion. Advanced GC development in patients with FAP implies a high malignant potential of GC in patients with FAP [45]. Therefore, careful follow-up is needed, even after endoscopic resection of GC in cases of recurrence, especially when precise histopathological evaluation is impossible.

This study has several limitations. First, this was a retrospective study conducted with a few patients in a tertiary center, to which patients with FAP and GNs were referred for endoscopic treatment or surgery. Therefore, the study design might have had selection bias and insufficient statistical power. Second, few patients underwent a serological, urea breath, or stool antigen test to check for \textit{H. pylori} infection. We considered the presence of atrophic gastritis as a surrogate marker for \textit{H. pylori} infection. Although endoscopic assessment of atrophic gastritis is useful for elucidating the \textit{H. pylori} infection status [46], establishing the effect of \textit{H. pylori} infection on tumorigenesis in patients with FAP requires verification using one of the aforementioned tests. Third, APC germline mutations were not analyzed in each patient. Furthermore, to understand the mechanism of GN development, studies investigating the role of somatic mutations and epigenetic alterations in GNs are necessary.

Together, our study highlights the necessity for routine surveillance of EGD in patients with FAP. GNs were more frequent in these patients. Nodule-type GNs often occurred in the upper body of the stomach in patients with FGPs, whereas depressed-type GNs mostly occurred in the lower body of the stomach in patients without FGPs. Although slightly elevated GNs were characteristic in both groups, such lesions were difficult to detect when they developed among FGPs. Thus, our study demonstrated the endoscopic features that should be considered during EGD surveillance in patients with and without FGPs. Interestingly, background mucosa and the type of GN present varied, even within the same pedigree. ESD was an effective and minimally invasive endoscopic treatment for GNs in patients with FAP. Although ESD seemed to be more appropriate than EMR, technical ingenuity might be necessary for GNs that develop into FGPs. Moreover, careful follow-up is essential, even after endoscopic resection, especially in patients with FGPs.

**ACKNOWLEDGMENTS**

The authors thank Dr. Yusuke Tani from the Division of Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences, for his valuable comments.

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