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Gastric Adenocarcinoma of the Fundic Gland Type: A Case Report

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Patient: **Male, 78-year-old**
Final Diagnosis: **Fundic gland adenocarcinoma**
Symptoms: **Tumor**
Medication: —
Clinical Procedure: —
Specialty: **Pathology**

Objective: **Rare coexistence of disease or pathology**

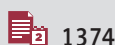
Background: Gastric adenocarcinoma of the fundic gland type (GAFG) is an extremely rare neoplasm that consists of a mixed proliferation of oxyntic and chief cells. Differential diagnosis of GAFG is difficult in the absence of infiltration. Here, we report a case of GAFG and discuss the clinicopathological features.

Case Report: A 78-year-old man was diagnosed with gastritis and reflux esophagitis, status after esophagectomy for carcinoma of the esophagus in 2015. The patient underwent repeated gastric biopsies in 2017 and an atypical epithelium was observed, but no diagnosis was confirmed. There was no evidence of tumor extension in the submucosa. The tumor was resected via endoscopic mucosal resection, and pathological examination was performed. Microscopic findings revealed an oxyntic-type gastric mucosa with atypical dense or dilated glands with abundant pale basophilic cytoplasm and round nuclei with prominent nucleoli. The majority of the tumor cells resembled chief cells, suggesting they were derived from gastric fundic glands. However, the tumor appeared to have no submucosal infiltration or focal stromal desmoplastic reaction. Sections stained positive for MUC6 and pepsinogen-I in chief cells, and H+/K+ ATPase and PDGFR α in parietal cells, but were mostly negative for CDX2, chromogranin A, synaptophysin, and CD10. Sections stained for mib-1 expressed very low proliferative activity, with an average of 10%. Staining for TP53 overexpression was negative.

Conclusions: Immunostaining markers are a supportive tool for histological diagnosis of GAFG. However, if there is no infiltration, as in our case, it is difficult to consider it as a malignant tumor. Further elucidation is needed in the future, including an officially accepted diagnostic name.

Keywords: **Histology • Immunohistochemistry • Stomach Neoplasms**

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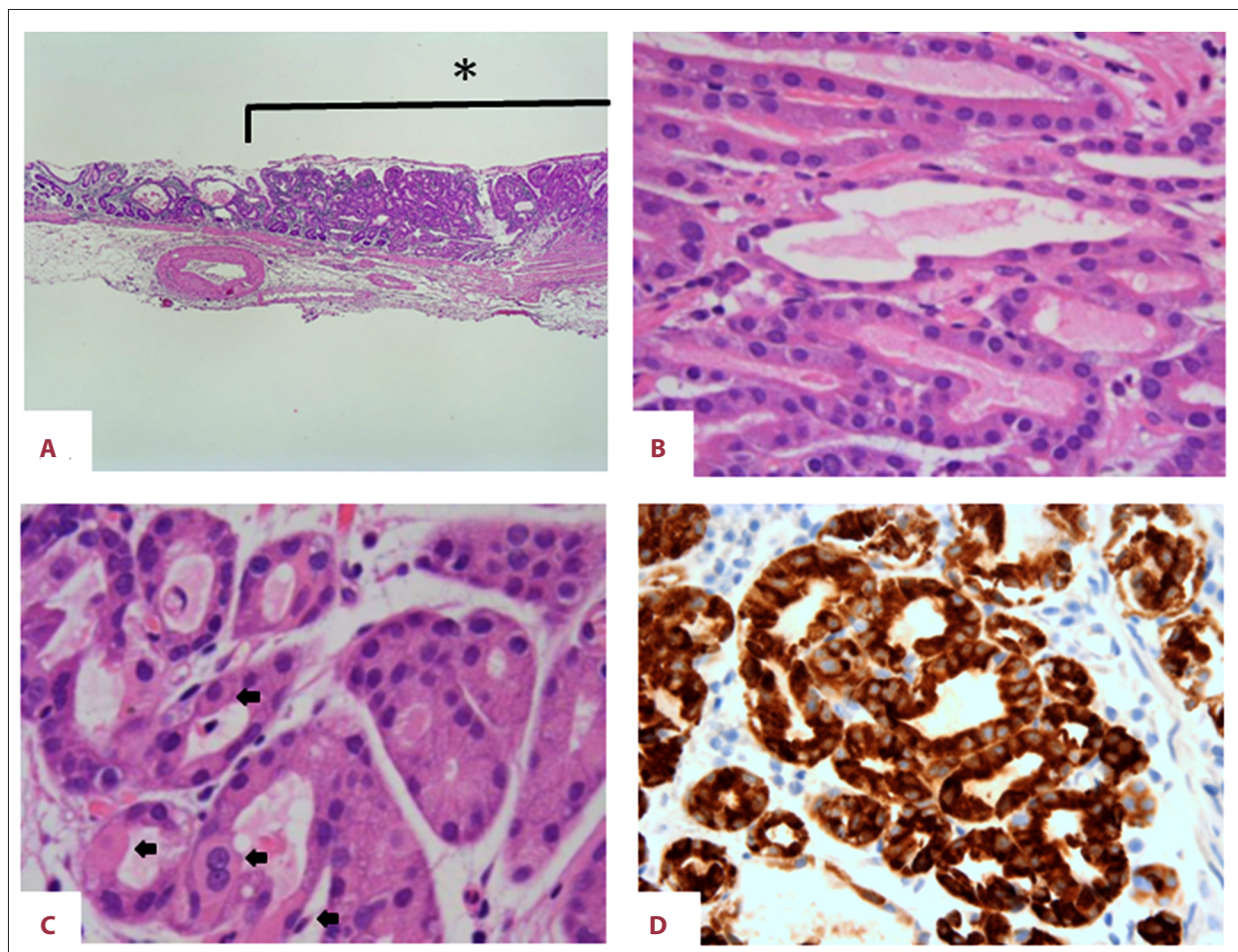


Background

Gastric adenocarcinoma of the fundic gland type (GAFG) is an extremely rare neoplasm composed of mixed growth of oxyntic and chief cells [1-12]. GAFG (chief cell-predominant type) was defined by Ueyama et al in a report of 10 cases [2]. They proposed that this type of gastric tumor consisted mainly of chief cells with nuclear atypia. They also reported this type of gastric tumor's non-aggressive behavior and how it is limited to the mucosa with minimal infiltration of the submucosa, and no lymphatic or venous invasion observed in 10 cases. Therefore, it is hypothesized that GAFG may be a benign tumor because of the lack of progression or recurrence. Singhi et al reported that the appellation oxyntic gland polyp/adenoma (OPA) was more suitable based on the tumor's non-aggressive behavior [3]. Mueller-Hocker et al reported a similar case with ultrastructural confirmation [4]. A recent review indicated that submucosal invasion is observed in only 57% of cases [5]. Therefore, differential diagnosis as GAFG is difficult in histological diagnosis. Here, we report a case of GAFG and discuss the clinicopathological features.

Case Report

A 78-year-old Japanese man was diagnosed with gastritis and reflux esophagitis, status after esophagectomy for carcinoma of the esophagus in 2015. Additionally, the patient's past medical record included hypertension (age 55 years), hydronephrosis (age 55 years), drinking 1 can of beer per day, and smoking 20 cigarettes per day from age 18 to 64 years. He was prescribed an H2 receptor blocker and this helped reduce his gastritis and reflux symptoms, although he only took it periodically. The patient underwent regular gastric biopsies from 2017 which detected an atypical epithelium, but no clear diagnosis was made. An endoscopic examination was carried out to pursue the possibility of endoscopic mucosal resection (EMR) of the tumor. A 12-mm brown, flat, elevated tumor in the body of the stomach was found. However, there was no evidence of submucosal infiltration. The tumor was resected by EMR, and a pathological examination was performed. The patient underwent a computed tomography (CT) scan in March 2020, which found no metastasis in the chest or abdominal organs. The endoscopy with biopsy was repeated 2 months after EMR and there was no evidence of any neoplasms.



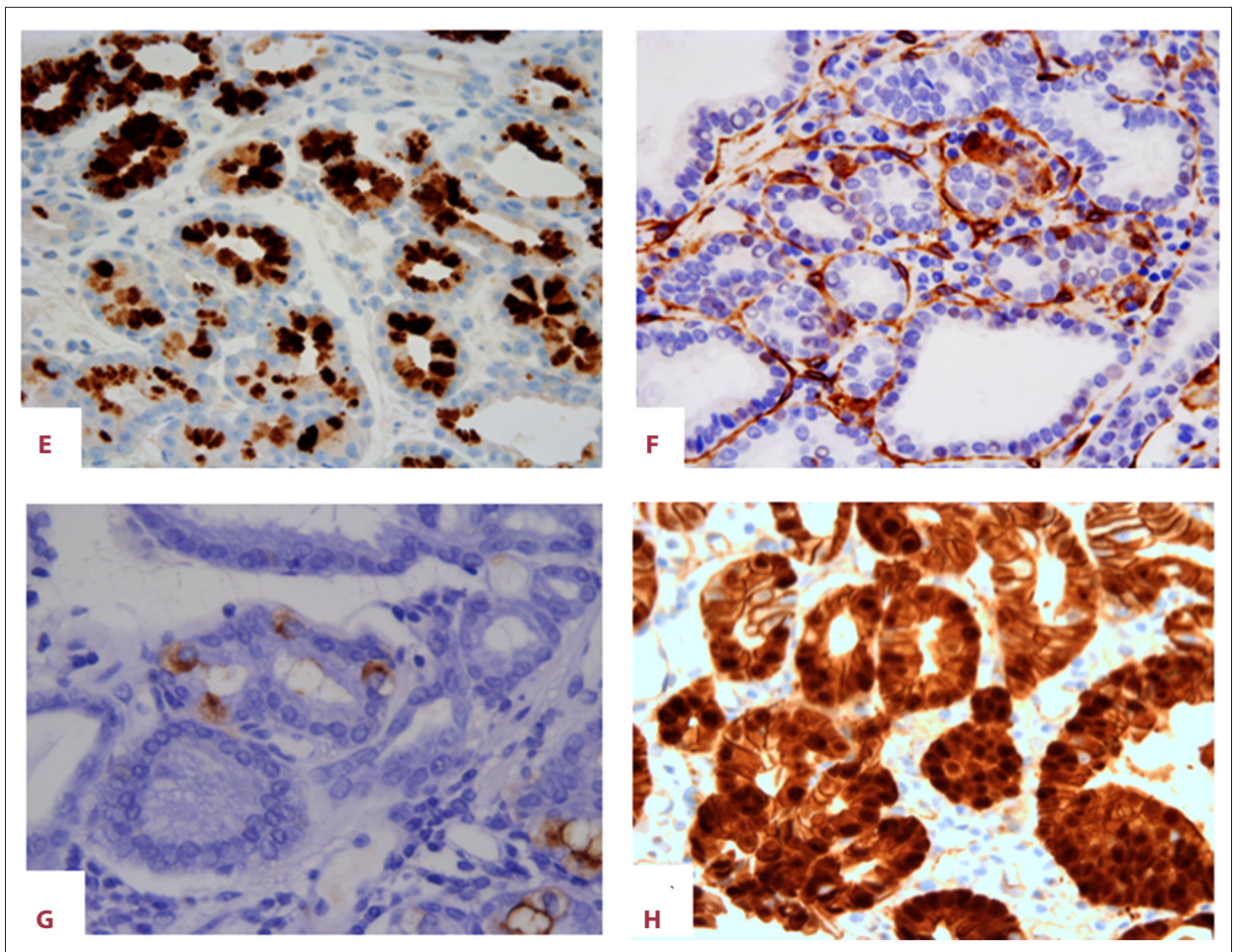


Figure 1. At low magnification, a gastric adenocarcinoma of the fundic gland type (GAFG) is located in the mucosa (A). The tumor consisted of clustered tumor cells resembling chief cells and cystic glands (B). At high magnification, it is clear that the tumor contains chief cells and parietal cells → (C). Immunohistochemically, the tumors are positive for MUC6 and pepsinogen-I in chief cells, H+/K+ ATPase and PDGFR α in parietal cells (D-G) and are focally strongly positive for β -catenin (H).

Microscopic findings revealed an oxyntic-type gastric mucosa with plentiful atypical dense or dilated glands with abundant pale basophilic cytoplasm and round nuclei with prominent nucleoli (Figure 1A, 1B). The majority of the tumor cells resembled chief cells (Figure 1C), suggesting they were derived from gastric fundic glands. Several scattered tumor cells with granular eosinophilic cytoplasm mimicking parietal cells were found in some part of the tumor. The tumor showed no infiltration into the submucosa, stromal desmoplastic reaction, or lymphovascular invasion. Some of these tumor glands were cystically dilated, while others were distorted. The gastric mucosa surrounding the tumor appeared to have mild edema with infrequent lymphoid infiltration. There was no *Helicobacter pylori* infection as confirmed by toluidine blue staining. We excluded the possibility of intestinal metaplasia and gastric atrophy, which are associated with classical gastric adenocarcinoma. Sections stained positive for MUC6 (Figure 1D), Pepsinogen-I (Figure 1E), PDGFR α (Figure 1F), H+/K+ ATPase (Figure 1G), and

nuclear β -catenin accumulation (Figure 1H), but were mostly negative for CDX2, chromogranin A, synaptophysin, and CD10. The mib-1 proliferative index showed very low activity, with an average of 10%. We did not find any TP53 overexpression. These histopathological findings are consistent with a fundic gland adenocarcinoma of the low-grade, chief cell-predominant type, as described by Ueyama et al [2].

Discussion

GAFG is a recent term for gastric lesions with a mixed growth of oxyntic and chief cells as defined by Ueyama et al. Our patient also had round to oval nuclei with prominent nucleoli. Nuclear atypia is considered to be a useful finding to distinguish cancer from benign disease. Nevertheless, Singhi et al reported that various degrees of nuclear atypia are present in OPA [3]. Therefore, it is difficult to distinguish between benign

and malignant tumors based solely on nuclear atypia. Ueyama et al reported that most of their 10 cases had mild desmoplasia. However, Singhi et al reported no necrosis or desmoplasia in their 10 cases, similar to our findings. In a larger series, Chan et al reported that 2 of 12 cases showed evidence of mild stromal desmoplasia with eradication of the lamina propria due to a mild fibroblastic reaction [6]. Only 1 case also had apoptotic luminal debris, but 11 had no necrosis. Due to the observations mentioned above and insufficient frequency, we could not confirm our diagnosis with repeated biopsy specimens; in the end, the diagnosis was confirmed by endoscopic surgery specimens.

Immunohistochemical staining is a practical and useful way to differentiate GAFG from other cancers. On immunohistochemical examination, our case was positive for MUC6 and pepsinogen-I in chief cells; H+/K+ ATPase and PDGFR α in parietal cells; and negative for CD10, with low mib-1 labeling and no p53 overexpression. These results suggest that this tumor had gastric phenotypic markers (chief cell, parietal cell), a low proliferation rate, and a mild clinical presentation compared with typical stomach cancer [2,11,12]. However, these results are similar not only to GAFG, but also to OPA cases. GAFG gastric tumors are less aggressive and are limited to the mucosa, with minimal involvement of the submucosa, and no lymphatic or venous invasion recognized. This is consistent with our case. A recent review reported that submucosal invasion is observed in 57% of cases [5].

Therefore, it is hypothesized that GAFG may be a benign tumor because of the low rates of progression or recurrence. Several reports have recognized GAFG as a cancer [7-9]. In contrast, Singhi et al reported that the term OPA was more appropriate because of this tumor's non-aggressive behavior [3]. Further, Chen et al advocated the term "chief cell-predominant gastric polyp" [7]. Although this reflects differences in diagnostic criteria for intramucosal lesions between Europe, America, and Japan, the current confusion warrants further analysis to show that intramucosal lesions are also cancerous.

CDX2 has a tumor suppressor role and is considered a key player in intestinal differentiation. CDX2 has been reported to be an important factor in the infiltration of gastric cancer of the intestinal type, and to have a good prognosis [13,14]. The CDX2-negative result in our case was an unexpected result because the infiltration and proliferation ability are reportedly not

marked in GAFG. However, similar to our findings, Chan et al reported that CDX2 was negative in all of their cases for which it was assessed (5 of 5) [6]. Therefore, it is considered that the tumor profile of GAFG differs in terms of tumorigenesis from that of typical gastric cancer.

In our case, we demonstrated that nuclear β -catenin expression was significantly higher than in normal fundic mucosa. In a previous article, β -catenin showed normal membranous staining without nuclear expression [3,15]. In contrast, conventional gastric adenocarcinoma is associated with nuclear β -catenin accumulation in 20% to 60% of cases [16,17]. Therefore, we were suspicious of malignancy for GAFG. However, β -catenin expression tends to be higher in not only GAFG with submucosal invasion (6%), but also OPA (26%) [1]. Accordingly, our speculation is that β -catenin activation may play an important role in GAFG, but we cannot confirm any malignancy. At present, there are no clear morphological or immunohistological findings to distinguish intramucosal GAFG from OPA.

Conclusions

GAFG is a newly identified tumor with unique histomorphology and low malignant potential. The tumor in this case report was positive for MUC6 and pepsinogen-I in chief cells, H+/K+ ATPase and PDGFR α in parietal cells, and nuclear β -catenin accumulation, but negative for CD10, with low mib-1 expression and no p53 overexpression, suggesting a different tumorigenesis pathway from that of common adenocarcinomas of the stomach. Immunostaining markers can be supportive tools for histological diagnosis. However, if there is no infiltration, as in our case, it is difficult to diagnose a malignant tumor. Further elucidation is needed in the future, including a consensus on the diagnostic name.

Acknowledgements

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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