Original Article
Endoscopic and clinicopathological features of gastric adenocarcinoma of fundic gland mucosa type: a case report and literature review

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Abstract: Background: Gastric adenocarcinoma of fundic gland mucosa type (GA-FGM) is a low-grade atypia and well-differentiated adenocarcinoma. Thus far, ten cases of GA-FGM have been reported in the literature. We report a case and discuss the clinicopathological features of GA-FGM to improve the understanding and diagnosis of GA-FGM. Methods: We retrospectively reviewed the clinical, endoscopic, histological, and immunophenotypic features and treatment of 1 case of GA-FGM, and combined this with literature discussion. Results: This is a 52-year-old male patient who underwent upper gastrointestinal endoscopy and was found to have a type IIc lesion on the upper part of the stomach. Most of the surface of the cancer tissue was covered with normal epithelium as observed under low magnification. The surface of the focal mucosa was covered with tumorous gastric pit epithelial cells. Deep tumors are mainly composed of a large number of eosinophils and a small number of gastric pit cells, which are mottled. Tumor cell nucleus showed mildly atypical characteristics with loss of nuclear polarity and visible nuclear fission. The glandular structure had significant atypia. Tumor invaded the submucosa. Immunohistochemistry showed that MUC5AC was positive on the surface and deep pit-epithelial-like tumor cells. The deep cancer tissues were widely positive for pepsinogen I (pepsin A) and H+/K+-ATPase, and some cancer cells expressed MUC6. The Ki-67 proliferation index was approximately 3%. Conclusions: GA-FGM is a rare new histological type of gastric cancer. The possibility of GA-FGM should be considered when the gastric intrinsic mucosal epithelial cells are mildly atypical and the fundic gland structure is markedly atypical and the distribution pattern of the relative normal mucosal immune phenotype was observed, especially in biopsy specimens.

Keywords: Gastric adenocarcinoma of fundic gland mucosa type, gastric adenocarcinoma of fundic gland type, endoscopic submucosal dissection

Introduction

Gastric adenocarcinoma of the fundic gland type (GA-FG) is a rare disease entity first reported by Tsukamoto et al [1] in 2007. GA-FG is a well-differentiated adenocarcinoma with mild nuclear atypia. In 2010, Ueyama et al [2] further confirmed that “GA-FG” is a low-grade malignancy, and the tumor mainly differentiates into mucous neck cells and chief cells; it also differentiates into parietal-type cells. They proposed GA-FG as a new entity of gastric adenocarcinoma. According to previous reports, GA-FG accounted for 0.98%-1.6% [3, 4] of gastric cancer cases, and the reported number of cases has kept increasing [5].

Recently, a “gastric adenocarcinoma of fundic gland mucosa type (GA-FGM)” [6] similar to “GA-FG” but with a different nomenclature has appeared. GA-FG mainly proliferates in the deeper layers of the mucosa, while the epithelium of the surface layer is a non-neoplastic region [2-5, 7-10]. In addition to fundic gland
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cell-like differentiation, a lesion showing MUC-5AC-positive foveolar epithelium-like differentiation is defined as “GA-FGM” [6]. Thus far, only ten cases of GA-FGM have been reported [6, 11-13]. In the present study, we report a case and discuss the clinicopathological features of GA-FGM with literature to improve the understanding and diagnosis of GA-FGM.

Case presentation

Clinical manifestation

A 52-year-old man who underwent upper gastrointestinal endoscopy (GIF-Q150, Olympus, Tokyo, Japan) for intermittent upper abdominal pain at a local hospital, and was found to have type IIc lesion (Figure 1A) on the small curved side of the upper part of the stomach. A biopsy was performed, and the pathological diagnosis was chronic inflammation of the gastric mucosa. The patient was admitted to our hospital in May, 2018. Physical examination revealed no abnormal finding in the chest and abdomen.

Auxiliary examination

Ordinary white light endoscopic (GIF-H260Z+ CV-290/CLV-290SL, Olympus, Tokyo, Japan) examination revealed that the lesion was clas-

Figure 1. GA-FGM under white light endoscope (A-C) and observed by magnified NBI (D-I). (A) A superficial depression type lesion is observed on the small curved side of the upper part of the stomach. (B) The marginal crypt epithelium (MCE) of close observation is elongated and disordered. Dendritic vessels are observed. (C) Indicarmin staining. The boundary of the lesion is not clear. (D) Clockwise enlargement of different color box areas. (E) Blood vessel tortuosity. (F) The MCE is long-lined and partially disappears. The upper glandular opening is pinhole-like. (G) Microvascular hyperplasia. (H) The elongated MCE has different lengths and directions. (I) The MCE is not clear and is partly in granular shape.
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sified as type IIc with a diameter of <10 mm. The lesion color was faded, and dendritic ves-
sels were readily visible. The marginal crypt epithe-
lum (MCE) was elongated with varying
lengths and directions (Figure 1B). The bound-
ary was not clear after spraying indicarmine
(concentration: 0.2%) (Figure 1C). Magnifying
narrow-band imaging (NBI) observation: The
lesion boundary was clear, abnormal vascular
morphology; some MCE disappeared, and so-
me MCEs were significantly elongated (Figure
1D-I). The background mucosal glandular open-
ing was pinhole-like, with no atrophy and intes-
tinal metaplasia.

The C-13 breath test was negative. Other blood
test results were normal. Abdominal computed
tomography examination showed no abnorma-
larities.

Treatment and follow-up

The lesion was judged to be an indicatio for
endoscopic submucosal dissection (ESD). After
the patient’s informed consent and signature,
ESD was performed for one-time complete re-
section. Endoscopic examination at 12 months
after ESD showed good healing results of the
original lesion areas.

Materials and methods

The tumor specimens were fixed in 10% neutral
formalin, then conventional paraffin sectioning
and hematoxylin and eosin (H&E) staining were
performed. The morphology of tumor tissue
was observed under a light microscope. The
Elivision-2 kit of immunohistochemistry were
provided by Maixin Biotech (catalog No. Kit-
5930, Fuzhou, China). The experimental pro-
cedures were carried out according to the instruc-
tions. The primary antibodies and their pre-
treatment methods are listed in Table 1.

Results

Pathological examination

Visual observation: A mucosal tissue, 28 mm ×
22 mm in size, with a type IIc lesion at 7 mm
from the proximal margin and with a size of 9
mm × 6 mm.

Histological morphology: The boundary of can-
cer tissue was clear, and some cancer tissue

Table 1. Antibodies used, their pretreatments, dilutions, and manufacturers

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Dilution</th>
<th>Pretreatment</th>
<th>Manufacturer</th>
</tr>
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<tbody>
<tr>
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<td>Ccp58</td>
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<td>Citric acid</td>
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<td>MUC5AC</td>
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<td>EDTA</td>
<td>Abcam, Boston, USA</td>
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<tr>
<td>H+/K+-ATPase</td>
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<td>1:400</td>
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<td>CD31</td>
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<tr>
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<tr>
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<td>CWWB1</td>
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<td>Desmin</td>
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<tr>
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<td>Ki-67</td>
<td>MIB-1</td>
<td>Ready to use</td>
<td>EDTA</td>
<td>Celnovte Biotech</td>
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</table>

*Antigen repair was performed at high temperature and high pressure using potassium EDTA (1 mM pH 9.0)/citric acid (0.01
M, pH 6.0) antigen repair fluid.
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Some gland structures were complex, and resembled “antler” or “ginger” (Figure 2E). The leading edge of the cancer tissue was infiltrated in an expanding growth pattern (Figure 2F).

The cancer cells were arranged in a columnar or high columnar shape. The most common was eosinophilic epithelial cells, which had a slightly enlarged nucleus in comparison to normal epithelium with a round to rod-like or irregularly shaped nucleus, with deep nuclear staining, fine and dense chromatin, and centralized distribution of the chromatin at the edge. These cancer cells had median amphoteric nucleoli, and nuclear division could be observed. Atypical nuclear division could also be observed. The polarity of the nucleus was disordered or lost. The nuclei were arranged in a crowded or even overlapping manner and located on the basal side. The cytoplasm was abundantly and obviously eosinophilic. In some areas, the polarity of cells was disordered. Another type of cells were pit-epithelial-like cells with a round or oval nucleus located on the basal side. The nucleus was slightly vacuolated. The chromatin was slender, sparse, with clear nucleoli; the cytoplasm was transparent or lightly stained; and the polarity of nucleus was disordered. The two types of cells appeared together in the same gland, or they were scattered and distributed in the same gland in a mottled condition (Figure 2G and 2H).

Proliferative mucosal muscles were observed between the tumor glands. There was no obvious fibrous connective tissue hyperplasia. A small number of lymphocytes, plasma cells, and eosinophils was observed. No necrosis, ulcers, or ulcer scars were observed. The mucosa around the lesion was close to the normal

Figure 2. GA-FGM. (A) The deeply stained area at the center is GA-FGM tissue (in the yellow box). The cancer tissue infiltrates the submucosa. The surface of the focal area is covered by cancer tissue (below the cyan line). (B) Dense hyperplasia of tumor glands. (C) The focal surface layer is covered with the tumorous epithelial cells, which are connected to the underlying cancer tissue. (D) The tumorous glands are inconsistent in direction, and the surface is covered with normal epithelial tissue. (E) The branched tubular gland is complex in structure and resembles an “antler” or “ginger”. (F) Thick-walled blood vessels (in the green circle) are visible in the cancer tissue. The front edge of the tumor grew in a expansive manner. (G) High magnification, the direction of the cancer cells are disordered, and loss of nuclear polarity, showing nuclear division (within the cyan circle). (H) The same gland is composed of eosinophilic epithelial cells and cytoplasmic translucent pit-epithelial-like cells, and showing mottled shape. The cancer cells are columnar, and nuclear division is observed (within the cyan circle). HE staining (A-H).

were located in the submucosa (Figure 2A and 2B). Most of the surface of the cancer tissue was covered with normal epithelium as observed under low magnification. The surface of the focal mucosa was covered with atypical gastric pit epithelial cells, and there was a band area with sparse regional glands under the epithelium (Figure 2C and 2D).

The morphology of the cancer tissue was relatively consistent. Branched tubular glands densely proliferated with disordered arrangement.
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MUC5AC was positive on the surface and deep pit-epithelial-like tumor cells. The deep cancer tissues were widely positive for pepsinogen I (pepsin A) and H+/K+-ATPase, and some cancer cells expressed MUC6. Desmin was significantly reduced in the mucosal muscle tissue within the lesion. Ki-67-positive cells were scattered and unevenly distributed with 3% in the highest area (Figures 3 and 4A-F). The proportion of Cyclin D1-positive cells was approximately 75%. The β-catenin membrane was positive, and no staining was observed in the nucleus. Synaptophysin, CD56, Chromogranin A, MUC2, CD10, CDX2, and Villin were negative; p53 was scattered with different strengths in a few positive cells, and tumor cells were not stained for c-erbB-2. CD31 and D2-40 showed no cancer infiltration in the lacunae of vessels and lymphatics, respectively, and Hp staining was negative.

Figure 3. GA-FGM immunohistochemical staining. MUC5AC-positive in pit epithelium and deep pit-epithelial-like tumors cells (A), partially cancerous MUC6-positive (B), and most cancer cells express pepsinogen I (C) and H+/K+-ATPase (D). Desmin staining showed a small amount of mucosal muscle remaining in the cancer tissue with an infiltration depth greater than 1000 µm (E). The Ki-67 proliferation index is approximately 3% (F).

Final pathological diagnosis was GA-FGM (Figure 4G). The pathological sections of preoperative biopsy conducted in another hospital were retrospectively reviewed (Figure 4H), and the histological morphology was the same as that of the ESD specimen.

Discussion

GA-FGM is a low-grade atypia and well-differentiated gastric adenocarcinoma, and is bidirectionally differentiated into the fundic gland and the pit epithelial cells. In this case report of GA-FGM, we found that both histomorphology and immunohistochemical staining showed that the very small area of the mucosal surface covered the tumorous epithelium and differentiated into the gastric pit epithelial cells. The cancer tissue located deep in the mucosa was dominated by gastric fundus adenocarcinoma cells, and two types of cancer cells, namely pit epithelium type and gastric fundic glandular type, were observed in the same tumorous gland.

Since its first discovery in 2015 [6] along with the cases reported by us, 11 more have been reported in the literature (Table 2) [6, 11-13]. GA-FGM is more common in older men with an average age of 67.2 years and a median age of 67 years (range 52-87 years). The male-to-female ratio is 2.7:1 (8:3). Most GA-FGM cases were diagnosed in the upper part of the stomach, followed by the middle part of the stomach. The average tumor diameter is 7.7 mm, and the median diameter is 6 mm (range 3-23 mm). According to the Paris classification, the most common type is 0-IIa type (6 cases), followed by 0-IIc type (2 cases) or 0-IIa+IIc type (2 cases); 0-I type is rare (1 case). In approximately 90% of cases, the tumor infiltrated into the submucosa layer, indicating that the tumor has a high tendency to infiltrate into the submucosa, which is similar to that of GA-FG [2-5, 7-9]. GA-FGM is one of the representative tumors of
Hp-negative gastric cancer, and it also occurs in Hp-positive gastric fundic mucosa (Table 2). GA-FGM is likely to be accidentally found during endoscopy examinations [6, 11, 12].

In this case, endoscopy revealed a clear tumor boundary, and the characteristic of the irregular microvascular and microsurface pattern [14], suggesting that it was a differentiated type of gastric cancer. Because most of the mucosal surface of the lesion was covered with normal epithelium, the lesion exhibited a fading color, which was similar to the submucosal tumor-like appearance of a carcinoid [15]. When the tumor was considered as lymphoma or undifferentiated carcinoma, it tended to infiltrate and destroy the epithelium of the glandular fossa. The white area was not distinguishable. In contrast, in the present case report, the glandular structure of GA-FGM remained intact. However, normal pit epithelial cells were replaced by tumor cells, and the white area was identifiable. In extremely rare cases, GA-FGM could occur in the submucosal ectopic glandular tissue, and the intrinsic mucosal tissue above the tumor was free of tumors [13]. Occasionally, GA-FGM could also occur with regular adenocarcinomas [12].

Cancer cells usually have mildly polymorphic or atypical nuclei with loss of nuclear polarity. The nucleus shows division and even atypical mitosis with obvious atypia in the glandular structure. Tumor infiltration destroyed mucosal muscles and invaded the submucosa, which could help to diagnose GA-FGM and distinguish it from benign gastric glandular polyps. Gastric pit epithelial cells were observed in the fundic glandular polyps, and sometimes, ectopic hyperplasia of the gastric pit epithelial cells was also observed. Currently, there are reports of gastric pit epithelial-type differentiated adenocarcinoma in sporadic fundic glandular polyps [16]. It is worth noting that there were no abnormalities in the glandular cells of the stomach. In addition to differentiation into gastric fundic cells, GA-FGM differentiated into pit-epithelial-like cells and covered the mucosal surface. Immunohistochemical staining could help to differentiate GA-FGM from GA-FG [2-5, 7-10].

In this case, eosinophilic tumors expressed MUC6, pepsinogen I, and H+/K+-ATPase, suggesting that these tumors differentiated into mucous neck cells/chief cells and parietal cells (differentiation of fundic gland). Tumor cells covering the mucosal surface and deep pit-epithelial-like cells expressed MUC5AC, indicating that these were gastric pit epithelial type tumors.
Table 2. Reported cases of GA-FGM

<table>
<thead>
<tr>
<th>Study (y)</th>
<th>Patient</th>
<th>Age (y)/Sex</th>
<th>Location</th>
<th>Tumor size (mm)</th>
<th>Macroscopic type</th>
<th>Invasive depth</th>
<th>H. pylori infection</th>
<th>Treatment</th>
<th>IHC Pep</th>
<th>Ki-67 LI</th>
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<tr>
<td>Tanabe (2015) [6]</td>
<td>1</td>
<td>54/male</td>
<td>U</td>
<td>6</td>
<td>0-IIa+IIC</td>
<td>pT1b</td>
<td>NA</td>
<td>ESD</td>
<td>Pep&gt;MUC6</td>
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<tr>
<td></td>
<td>2</td>
<td>60/male</td>
<td>U</td>
<td>9</td>
<td>0-IIa+IIC</td>
<td>pT1b</td>
<td>Negative</td>
<td>ESD</td>
<td>Pep&gt;MUC6</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>66/male</td>
<td>U</td>
<td>6</td>
<td>0-IIa</td>
<td>pT1b</td>
<td>Negative</td>
<td>ESD</td>
<td>Pep&gt;MUC6</td>
<td>5%</td>
</tr>
<tr>
<td></td>
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<td>67/female</td>
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<td>6</td>
<td>0-IIa</td>
<td>pT1b</td>
<td>NA</td>
<td>ESD</td>
<td>Pep&gt;MUC6</td>
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<td></td>
<td>5</td>
<td>67/female</td>
<td>U</td>
<td>7</td>
<td>0-IIa</td>
<td>pT1b</td>
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<td>7</td>
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<td>Takahashi (2017) [12]</td>
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<td>87/male</td>
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<tr>
<td>Our case (2018)</td>
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<td>52/male</td>
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</table>


Because of the small atypia of tumor cells and the similarity of histomorphology and immunophenotype to normal gastric mucosa, GA-FGM is easily misdiagnosed as non-neoplastic lesions, especially in the diagnosis of biopsy specimens. Therefore, glands with mild atypical cells should be observed for architectural atypia and invasive behavior. This is the main point of GA-FGM diagnosis. Because only a few tumors are exposed to the mucosal surface and differentiate into pit epithelium, so experienced pathologists may misdiagnose GA-FG. In order to prevent misdiagnosis of this kind of lesion, it is necessary to master its endoscopic and clinicopathological features. We provide a good learning case. The pathogenesis of GA-FGM is still unclear. Further study is needed to investigate whether the overexpression of cyclin D1 protein in our case could be related to the occurrence and development of tumors in the further time period.

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Disclosure of conflict of interest

None.

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In the study, we focused on gastric adenocarcinoma of fundic gland type. Stomach Intestine 2015; 50: 1469-1479. (In Japanese).


