New type of gastric carcinoma / adenocarcinoma of fundic gland type: Its clinicopathological feature and tumor development

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New type of gastric carcinoma / adenocarcinoma of fundic gland type (GAC-FG): Its clinicopathological feature and tumor development

1. Proposal for new entity: gastric adenocarcinoma of fundic gland type (GAC-FG)
2. Clinicopathological feature of GAC-FG
3. Tumor progression of GAC-FG
4. Differential diagnosis
Endoscopic feature: 0–IIa−IIc

Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Histological feature
Variation of cytologic features
We proposed a new entity:
Gastric adenocarcinoma of fundic gland type
Previous reports of gastric adenocarcinoma with chief cell differentiation

Only one case report by Tsukashita et al. had been reported before our report.
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Materials and methods

Group A

Adenocarcinoma of fundic gland type pepsinogen-I (+) = 10 lesions

Clinicopathological features

Immunohistochemical evaluation (cell differentiation, biologic behavior)

Group B

Adenocarcinoma, well differentiated pepsinogen I (+) = 2 /111 lesions (1.8%)
Clinicopathological features of adenocarcinoma of fundic gland type (Group A)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42-79 (average :66)</td>
</tr>
<tr>
<td>Gender</td>
<td>M : F = 6 : 4</td>
</tr>
<tr>
<td>Location</td>
<td>U : M : L = 10 : 0 : 0</td>
</tr>
<tr>
<td>Size</td>
<td>4-20 (average :8.6) mm</td>
</tr>
<tr>
<td>Macroscopic</td>
<td>IIa : IIb : IIc = 5 : 0 : 5</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td>M : SM = 1 : 9</td>
</tr>
<tr>
<td>Lymph node metastasis (ly)</td>
<td>(-)</td>
</tr>
<tr>
<td>Vascular invasion (v)</td>
<td>(-)</td>
</tr>
<tr>
<td>Lymph node metastasis (LN)</td>
<td>0/1 (not examined in 9)</td>
</tr>
</tbody>
</table>
Clinicopathological features

Clinical
- Location: upper stomach
- Invasion into submucosa in early phase
- No recurrence or metastasis
- (follow up 10〜70 months / average 37 months)

Pathological
- composed of fundic gland-like cells,
  mainly of chief cells with pepsinogen I (+)
- irregularly arranged and anastomosing glands
- No lymphovascular invasion (ly0, v0)
- p53(-), Low MIB-1 index
- Immunohistochemistry -

Cell differentiation

MUC2  (goloblet cells)
MUC5AC (foveolar cells)
MUC6  (pyloric glands / neck cells)
CD10  (brush border)
pepsinogen-I (chief cells)
H+/K+-ATPase (parietal cells)
Chromogranin-A  (neuroendocrine)

Ki-67 (MIB-1)
p53

Biological behavior
Gastric adenocarcinoma of fundic gland type

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUC2</td>
<td>0/10</td>
</tr>
<tr>
<td>MUC5AC</td>
<td>1/10</td>
</tr>
<tr>
<td>MUC6</td>
<td>10/10</td>
</tr>
<tr>
<td>CD10</td>
<td>0/10</td>
</tr>
<tr>
<td>Pepsinogen-I</td>
<td>10/10</td>
</tr>
<tr>
<td>H+/K+-ATPase</td>
<td>4/9 *</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>0/10</td>
</tr>
</tbody>
</table>

* not diffusely positive, less than 20%
Case 6

- MUC2 (-)
- MUC5AC (-)
- MUC6 (+)
- CD10 (-)
- pepsinogen-I (+)
- H+/K+-ATPase (+)
- p53 (-)
- Ki-67 (1.7%)
- Chromogranin-A (-)
Clinicopathological features of pepsinogen-I(+) gastric adenoarcinoma (Group B)

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Lower part</td>
<td>Lower part</td>
</tr>
<tr>
<td>Size</td>
<td>25x35mm</td>
<td>20x17mm</td>
</tr>
<tr>
<td>Macro</td>
<td>Type 5</td>
<td>0-IIc</td>
</tr>
<tr>
<td>Histology</td>
<td>tub2&gt;tub1</td>
<td>tub1</td>
</tr>
<tr>
<td>Depth</td>
<td>SM (2100μm)</td>
<td>SM (500μm)</td>
</tr>
<tr>
<td>Ly, v</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>LN meta</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Gastrointestinal phenotype</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>Ki-67 LI</td>
<td>26%</td>
<td>21%</td>
</tr>
</tbody>
</table>
CD10 (+)
MUC2 (-)
MUC5AC
MUC6 (+)
pepsinogen-1 (+)
H+/K+-ATPase (-)
p53 (-)
Ki-67 (26%)
Chromogranin-A (-)
Clinicopathological features of Group B: pepsinogen-I(+) gastric adenocarcinoma

- **Location**
  - Lower part of stomach

- **Histological feature**
  - Common adenocarcinoma
  - not similar to fundic glands

- **Immunohistochemistry**
  - Focal positive for pepsinogen-I
  - Gastro-intestinal mixed phenotype
  - High Ki-67 Labeling index

Adenocarcinoma of fundic gland type
New type of gastric carcinoma / adenocarcinoma of fundic gland type (GAC-FG): Its clinicopathological feature and tumor development

1. Proposal for new entity: gastric adenocarcinoma of fundic gland type (GAC-FG)
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Gastric adenocarcinoma with pepsinogen-I(+) 

27 lesions (from 25 patients)

Group A: 10 lesions from AJSP 2010

Group B: 10 lesions after AJSP 2010

Group C: 7 lesions (5 patients) from Dr Kushima
More cases were summarized in this paper. Totally, 27 cases were collected.
The surrounding mucosa of the carcinoma

23/27 (85%) : almost normal fundic gland mucosa

4 /27 (15%) : accompanied by chronic inflammation

No relationship to H. pylori infection
### Comparison of clinicopathological features

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=10)</th>
<th>Group B (n=10)</th>
<th>Group C (n=5)</th>
<th>Total (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (average)</strong></td>
<td>66yrs</td>
<td>68yrs</td>
<td>67yrs</td>
<td>67yrs</td>
</tr>
<tr>
<td><strong>Gender (M : F)</strong></td>
<td>6 : 4</td>
<td>7 : 3</td>
<td>3 : 2</td>
<td>16 : 9</td>
</tr>
<tr>
<td><strong>Location (L : M : U)</strong></td>
<td>0 : 0 : 10</td>
<td>0 : 4 : 6</td>
<td>0 : 0 : 7</td>
<td>0 : 4 : 23</td>
</tr>
<tr>
<td><strong>Macroscopic feature (I : IIa : IIb : IIc : IIa+IIc)</strong></td>
<td>0 : 6 : 0 : 4 : 0</td>
<td>1 : 3 : 2 : 3 : 1</td>
<td>0 : 5 : 0 : 1 : 1</td>
<td>1 : 14 : 2 : 8 : 2</td>
</tr>
<tr>
<td><strong>Size (largest diameter)</strong></td>
<td>8.6mm</td>
<td><strong>15.3mm</strong></td>
<td>12.8mm</td>
<td>12.2mm</td>
</tr>
<tr>
<td><strong>Depth of invasion (M : SM)</strong></td>
<td>1 : 9</td>
<td>4 : 6</td>
<td>0 : 7</td>
<td>5 : 22</td>
</tr>
<tr>
<td>l(y (+))</td>
<td>0%</td>
<td>20%</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>v(+)</td>
<td>0%</td>
<td><strong>10%</strong></td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>
The smallest one
Located in

The smallest one
Case 6, 8mm
松山日赤症例：62歳、男性、0-IIc、SM (1200 μm)
68F, 31mm, 0-IIc, SM2(1.2mm), ly(+), v(-)
• High N/C ratio
• Ki–67 Index = 11%
• Multifocal SM invasion
• ly(+) 

Probably high-grade malignancy
Polypoid growth

Growing in deep mucosa at periphery

10mm
Polypoid growth 19mm
<table>
<thead>
<tr>
<th></th>
<th>Group A (n=10)</th>
<th>Group B (n=10)</th>
<th>Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pepsinogen-I</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>H⁺/K⁺-ATPase</td>
<td>44% *</td>
<td>40%</td>
<td>42% *</td>
</tr>
<tr>
<td>MUC5AC</td>
<td>10%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>MUC6</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>MUC2</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>CD10</td>
<td>0%</td>
<td>30% #</td>
<td>15%</td>
</tr>
<tr>
<td>chromogranin A</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Not examined for one lesion.
# Partially positive.
Adenocarcinoma of fundic gland type (Mixed chief and parietal cells variant)

Both antibodies are positive

Pepsinogen I (+)  \[ \text{H}^+ / \text{K}^+ \text{--ATPase} \, (+) \]
CD10 was partly expressed during progression
Proliferative activity

Ki-67 labeling index = average 6% (1 ~ 15%)

P53 protein overexpression

Only one lesion (1/20=5%)
Arising from deep mucosa

- Polypoid
- Minor root
- Flat

- Low-grade
- Main

- Elevated lesion with depression

- High-grade
- CD10(+)

- Depressed lesion with elevation at periphery
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Differential diagnosis

- Fundic gland polyp
- (Atypical) chief cell hyperplasia
- Adenoma of pyloric gland type
- Carcinoid tumor
- Parietal cell carcinoma
- Oncocytic adenocarcinoma
- Paneth cell carcinoma
Chief cell hyperplasia?

  Chief cell proliferation of the gastric mucosa mimicking early gastric cancer: an usual variant of fundic gland polyp.

  Chief cell hyperplasia with structural and nuclear atypia: a variant of fundic gland polyp.
  *Pathol Res Pract 200: 817-821, 2005*

The histological assessment only by biopsy

A possibility of carcinoma can not be denied.
Chief cell hyperplasia with structural and nuclear atypia: a variant of fundic gland polyp

Akihiro Matsukawa\textsuperscript{a,}\textsuperscript{*}, Ryoichi Kurano\textsuperscript{b}, Takahiro Takemoto\textsuperscript{c}, Motoko Kagayama\textsuperscript{a}, Takaaki Ito\textsuperscript{a}

**Fig. 2.** The polyp in the fundus: (a) The polyp in the superficial part represents cystic dilatations (H\&E stain). (b) The deeper glands in the fundus polyp show irregular branched tubules with nuclear stratification, proliferating to submucosa. Despite nuclear atypia, mitotic figures are absent (H\&E stain). (c) MIB-1 staining shows that proliferation activity of the cells is relatively low.
Differential diagnosis

• Fundic gland polyp
• (Atypical) chief cell hyperplasia
• Adenoma of pyloric gland type
• Carcinoid tumor
• Parietal cell carcinoma
• Oncocytic adenocarcinoma
• Paneth cell carcinoma
Oncocytic Adenocarcinoma of the Stomach
Parietal Cell Carcinoma

Kaiyo Takubo, M.D., Naoko Honma, M.D., Motoji Sawabe, M.D.,
Tomio Arai, M.D., Naotaka Izumiyama-Shimomura, Ph.D.,
Makoto Kammori, M.D., Koji Sasajima, M.D., and Yukiyoshi Esaki, M.D.

H⁺/K⁺−ATPase (−)
Anti-mitochondrial AB (+)


FIG. 2. High-magnification view of a relatively well-differentiated area of gastric carcinoma. The tumor cells have eosinophilic, finely granular cytoplasm and atypical nuclei with very prominent nucleoli (original magnification ×400).

FIG. 7. Tumor cells are strongly positive with antimitochondrial antibody MAB 1273, but the gastric surface epithelium and pyloric glands react much more weakly (original magnification ×200).
Parietal Cell Carcinoma of Gastric Cardia: Immunophenotype and Ultrastructure

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TABLE 2 Immunoreactivity of Parietal Cell Carcinoma

<table>
<thead>
<tr>
<th>Antibodies to:</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H^+/K^+$-ATPase</td>
<td>+++</td>
</tr>
<tr>
<td>Human milk fat globule-2</td>
<td>+++</td>
</tr>
<tr>
<td>Human foveolar gastric mucin</td>
<td>-</td>
</tr>
<tr>
<td>Muc-1 glycoprotein</td>
<td>+</td>
</tr>
<tr>
<td>Muc-2 glycoprotein</td>
<td>+</td>
</tr>
<tr>
<td>Muc-5AC glycoprotein</td>
<td>-</td>
</tr>
<tr>
<td>Muc-6 glycoprotein</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
</tr>
<tr>
<td>PCNA</td>
<td>-</td>
</tr>
<tr>
<td>P53</td>
<td>40% positive cells</td>
</tr>
</tbody>
</table>

FIG. 2 Light micrographs showing (A) poorly differentiated adenocarcinoma with solid growth pattern and focal micro-glandular structure, ×36; (B) abundant eosinophilic, finely granular cytoplasm, ×360; and (C, D) extensive lymphatic invasion, ×36, ×360.
AC of fundic gland type: The cytologic feature is often similar to that of Paneth cells.
Differential diagnosis

- Fundic gland polyp
- (Atypical) chief cell hyperplasia
- Adenoma of pyloric gland type
- Carcinoid tumor
- Parietal cell carcinoma
- Oncocytic adenocarcinoma
- Paneth cell carcinoma
A case submitted as “A case of gastric carcinoid”
Diagnosed as carcinoid by immunohistochemistry

Chromogranin A (CG-A)  
(-)

CD 5 6 & synaptophysin  
(+)

CG-A

CD 5 6  synaptophysin
GASTRIC ADENOCARCINOMA OF FUNDIC GLAND TYPE (CHIEF CELL PREDOMINANT TYPE) TREATED WITH ENDOSCOPIC ASPIRATION MUCOSECTOMY

HIROTOSHI FUKATSU,¹² HARUKA MIYOSHI,² KUNIHARU ISHIKI,² MAIKO TAMURA³ AND TAKASHI YAO⁴

¹Department of Internal Medicine, Himeji Red Cross Hospital, Himeji, ²Department of Internal Medicine, Nippon Kokan Fukuyama Hospital, Fukuyama, ³Department of Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama and ⁴Department of Human Pathology, Juntendo University School of Medicine, Tokyo, Japan
Summary

- Gastric adenocarcinoma of fundic gland type is a new entity.
- Immunostains of MUC6, pepsinogen I, H⁺/K⁺–ATPase are useful for diagnosis.
- It was originally reported as low-grade malignancy, however, some of them can progress into high-grade malignancy with phenotypic alteration.
- Further study with collecting more cases is needed for clarifying its natural history.
胃と腸で発表27例
+ その後の11例
= 38例