Retrospective Study

Clinical pathological features of alpha-fetoprotein producing early gastric cancer with enteroblastic differentiation

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AIM
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METHODS
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Abstract

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METHODS
We retrospectively investigated data on 6 cases of early stage GCED and 186 cases of early stage conventional gastric cancer (CGC: well or moderately differentiated adenocarcinoma) who underwent endoscopic submucosal dissection or endoscopic mucosal resection from September 2011 to February 2015 in our hospital.
GCED was defined as a tumor having a primitive intestine-like structure composed of cuboidal or columnar cells with clear cytoplasm and immunohistochemical positivity for either alpha-fetoprotein, Glypican 3 or SALL4. The following were compared between GCED and CGC: age, gender, location and size of tumor, macroscopic type, ulceration, depth of invasion, lymphatic and venous invasion, positive horizontal and vertical margin, curative resection rate.

RESULTS
Six cases (5 males, 1 female; mean age 75.7 years; 6 lesions) of early gastric cancer with a GCED component and 186 cases (139 males, 47 females; mean age 72.7 years; 209 lesions) of early stage CGC were investigated. Mean tumor diameters were similar but rates of submucosal invasion, lymphatic invasion, venous invasion, and non-curative resection were higher in GCED than CGC (66.6% vs 11.4%, 33.3% vs 2.3%, 66.6% vs 0.4%, 83.3% vs 11% respectively, P < 0.01). Deep submucosal invasion was not revealed endoscopically or by preoperative biopsy. Histologically, in GCED the superficial mucosal layer was covered with a CGC component. The GCED component tended to exist in the deeper part of the mucosa to the submucosa by lymphatic and/or venous invasion, without severe stromal reaction. In addition, Glypican 3 was the most sensitive marker for GCED (positivity, 83.3%), immunohistochemically.

CONCLUSION
Even in the early stage GCED has high malignant potential, and preoperative diagnosis is considered difficult. Endoscopists and pathologists should know the clinicopathological features of this highly malignant type of cancer.

Key words: Alpha-fetoprotein-producing gastric cancer; Gastric cancer with enteroblastic differentiation; Early gastric cancer; Glypican 3; SALL4

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Table 1  Clinicopathological findings for patients with gastric cancer with enteroblastic differentiation

| Case | 1 | 2 | 3 | 4 | 5 | 6 |
|------|---|---|---|---|---|---|
| Age, yr | 61 | 77 | 78 | 75 | 80 | 83 |
| Male/female | Male | Male | Male | Male | Female | Male |
| Tumor location: U/M/L | L | M | U | U | L | M |
| Tumor size, mm | 8 | 11 | 14 | 18 | 6 | 36 |
| Macroscopic type | 0-IIc | 0-IIc | 0-IIc | 0-IIa | 0-IIc | 0-IIa + I |
| Procedure method | HPtigG+ ESD | HPtigG+ ESD | HPtigG- ESD with additional surgery | N/A | HPtigG+ ESD | HPtigG+ ESD with additional surgery |
| Depth of invasion (µm) | M | SM (1500) | SM (1000) | SM (200) | M | SM (2000) |
| Lymphatic invasion | (-) | (+) | (-) | (+) | (-) | (+) |
| Venous invasion | (-) | (+) | (+) | (+) | (-) | (+) |
| Observation period (mo) | 51, ANED | 42, ANED | N/A | 38, ANED | N/A | 28, ANED |

Immunohistochemical analysis

- AFP (+) (-) (-) (+) (-) (+) (-)
- Glypican3 (+) (+) (+) (+) (+) (+) (-)
- SALL4 (+) (-) (-) (+) (+) (+) (-)
- MUC2 (-) (-) (-) (+) (-) (-) (-)
- MUC5AC (-) (-) (-) (+) (+) (+) (-)
- MUC6 (-) (+) (+) (+) (+) (+) (-)
- CD10 (+) (+) (+) (+) (+) (+) (-)
- P53 (-) (-) (-) (+) (+) (+) (-)

U: Upper third of stomach; M: Middle third of stomach; L: Lower third of stomach; H. pylori: Helicobacter pylori; IgG: Immunoglobulin G; ESD: Endoscopic submucosal dissection; M: Mucosa; SM: Submucosa; ANED: Alive with no evidence of disease; N/A: Not applicable; AFP: Alpha-fetoprotein.

Table 2  Results of comparison between patients with gastric cancer with enteroblastic differentiation and conventional gastric cancer n (%)

| GCED | CGC | P value |
|------|-----|---------|
| Number of lesions, n | 6 (2.7) | 209 (97.3) | N/A |
| Age, yr; median (range) | 75.7 (61-83) | 72.7 (40-92) | 0.39 |
| Male/female | 5/1 | 139/47 | 0.63 |
| Tumor location: U/M/L | 2/2/2 | 23/91/95 | 0.24 |
| Tumor size, mm; mean (range) | 15.0 (6-36) | 15.2 (2-60) | 0.96 |
| Macroscopic type: elevated type/flattened or depressed type | 2/4 | 92/117 | 0.60 |
| Ulceration | 0 | 19 (9.0) | 0.43 |
| Depth of invasion: M/SM | 2/4 | 185/24 | <0.01 |
| Rate of submucosal invasive cancer | 66.60% | 11.40% | |
| Median SM invasive depth, µm (range) | 1500(200-2000) | 795.8(100-5000) | 0.40 |
| Lymphatic invasion | 2 (33.3) | 5 (2.3) | <0.01 |
| Venous invasion | 4 (66.6) | 1 (0.4) | <0.01 |
| Positive horizontal margin | 0 | 9 (4.3) | 0.60 |
| Positive vertical margin | 1 (16.7) | 5 (2.3) | <0.05 |
| Curative resection1 | 1 (16.7) | 186 (89.0) | <0.01 |

The following is a comparison only for SM invasive cancer

| Number of SM invasive lesions, n | 4 | 24 | N/A |
| Lymphatic invasion | 1 (25) | 5 (20.8) | 0.88 |
| Venous invasion | 4 (100) | 1 (4.2) | <0.01 |
| Positive horizontal margin | 0 | 1 (4.2) | 0.33 |
| Positive vertical margin | 1 (16.7) | 2 (8.3) | 0.55 |
| Curative resection1 | 0 | 12 (50) | <0.01 |

1Curative resection was according to Gastric Cancer Treatment Guidelines 2010 or 2014 provided by the Japanese Gastric Cancer Association. GCED: Gastric cancer with enteroblastic differentiation; CGC: Conventional gastric cancer (well or moderately differentiated carcinoma); U: Upper third of stomach; M: Middle third of stomach; L: Lower third of stomach; Mucosa; SM: Submucosa.

Statistical analyses were conducted using SPSS (version 15.0 for Windows; SPPS Inc., Chicago, IL, United States) software. The comparison of clinicopathological features between GCEDs and CGCs were examined by the χ² test and the Mann-Whitney U test. The level of significance was set at P < 0.05.

RESULTS

This study included 192 cases (144 males, 48 females; mean age 72.8 ± 7 years; 215 lesions) of early stage GCED and CGC. Among 192 cases, there were 6 GCED cases (5 males, 1 female; mean age 75.7 years; 6 lesions) and 186 CGC cases (139 males, 47 females; mean age 72.7 years; 209 lesions). Table 1 shows the clinicopathological findings of the patients with GCED and Table 2 shows results of the comparison between patients with GCED and CGC. Four cases who were checked for Helicobacter pylori (H. pylori) infection by H. pylori-immunoglobulin G were positive. No significant differences were observed in tumor intestine-like structure composed of cuboidal or columnar cells with clear cytoplasm and immunohistochemical positivity for either alpha-fetoprotein (AFP) (rabbit polyclonal, 1:1000; Dako, Glostrup, Denmark), Glypican 3 (clone 1G12, 1:200; BioMosaics, Burlington, VT, United States) or SALL4 (clone 6E3, 1:100; Abnova, Taipei, Taiwan). Results of histology and immunohistochemical staining were evaluated by two pathologists specialized in the gastrointestinal tract. We determined curative resection criteria according to Gastric Cancer Treatment Guidelines 2010 or 2014 provided by the Japanese Gastric Cancer Association[5,6].

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to combinations of the expression of CD10, MUC2, and two as the intestinal type (2/6; 33.3%) according to combinations of the expression of CD10, MUC2, and MUC5AC, and MUC6 (Figure 3).

**DISCUSSION**

AFP was initially found in 1956 and is a fetal serum protein produced mainly in the fetal liver and yolk sac. After birth, AFP rapidly disappears and is not detected in the serum of healthy adults[7]. The serum level of AFP is increased in some patients with hepatocellular carcinoma (HCC) or yolk sac tumor. In clinical practice, AFP has been considered to be a useful tumor marker in screening or monitoring patients with HCCs or yolk sac tumors. However, some diseases other than HCCs and yolk sac tumor were also associated with high serum levels of AFP, and gastric cancer is one of the most common[2,8-15]. Since the first report of AFP-producing gastric carcinoma by Bourreille et al[16] in 1970, many cases have been reported, and the specifics of this disease have been gradually clarified.

Histologically, typical AFP-producing gastric carcinoma (AFP-producing gastric carcinoma) has been frequently reported as hepatoid adenocarcinoma[17-20]. However, there are also histologic types of carcinoma other than hepatoid adenocarcinoma. In 1994, Matsunou et al[21] reported two cases of AFP-producing gastric carcinoma with enteroblastic differentiation (AFP-producing clear cell gastric carcinoma), and the tumor characteristics were as follows: (1) columnar carcinoma cells growing primarily in tubulopapillary and glandular patterns; (2) abundant glycogen, but no mucin production in the clear cytoplasm; (3) gut hormone-containing cells scattered among clear carcinoma cells; (4) carcinoma cells producing oncofetal glycoproteins such as AFP and CEA; and (5) ultrastructurally, carcinoma cells showing well-developed microvilli with core filaments, whose rootlets formed occasional terminal webs, consistent with absorptive epithelium of fetal intestine or enteroblastic differentiation. Motoyama et al[22] proposed that AFP-producing gastric carcinoma should be divided into three subtypes: (1) hepatoid type; (2) yolk sac type; and (3) enteroblastic type. In the present study, we examined the clinicopathological features of 6 cases of gastric cancer with enteroblastic differentiation (GCED) and compared them with 6 cases of conventional gastric adenocarcinoma (CGC). GCED is defined as gastric carcinoma, whose rootlets formed occasional terminal webs, consistent with absorptive epithelium of fetal intestine or enteroblastic differentiation. The curative resection rate was significantly higher in GCED than CGC (100% vs 50%, P < 0.01). In 2 of the 6 GCED cases, additional surgery was performed (case 3: T1N0M0, stage IA; case 6: T1N1M0, stage IIA). Recurrence or metastasis was not seen in any of the 4 GCED cases that were followed from 28 to 51 mo (median 40 mo).

Histological examination of GCED demonstrated the presence of tubulopapillary carcinoma with clear cytoplasm at the deeper part of the mucosa and submucosa by lymphatic and/or venous invasion, and there was no severe stromal reaction. In all GCED cases, the superficial mucosal layer was covered with the intestinal type (2/6; 33.3%) according to combinations of the expression of CD10, MUC2, MUC5AC, and MUC6 (Figure 3).
The fetal gastrointestinal type is thought to be equivalent to GCED\cite{1,3}. It is said that most AFPGCs have various mixtures of these histologic types and CGC. Kinjo et al\cite{2} also reported that in a histologic type of submucosal invasive cancer of AFPGC, the positivity rates for CGC and GCED in the mucosal component were significantly higher than in the invasive component. On the other hand, hepatoid gastric carcinoma (HGC) was significantly positive in the invasive component. In this study, pathological findings in all GCED cases showed that the mucosal layer was composed of conventional tubular

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**Figure 2** Histological examination of the resected specimens with hematoxylin and eosin stain (case 1). A and B: The superficial mucosal layer was covered with a well differentiated adenocarcinoma; B-D: Carcinoma cells with clear cytoplasm had tubulopapillary growth, resembling the primitive gut. These carcinoma cells arose from the deeper part of the mucosal layer and invaded into the submucosal layer by venous invasion. There was no severe stromal reaction at the submucosal layer. Pathological diagnosis was as follows: stomach (ESD): adenocarcinoma with enteroblastic differentiation, 0-IIc, 11 mm × 9 mm, well-differentiated carcinoma > moderately-differentiated carcinoma, papillary adenocarcinoma, SM (1500 µm), ly (-), v (+), HM0, VM0. SM: Submucosa; ESD: Endoscopic submucosal dissection.

**Figure 3** Immunohistochemical examination of resected specimens (case 1). A: MUC2; B: MUC5AC; C: MUC6; D: CD10; E: AFP; F: Glypican 3; G: SALL4. The lesion had focal positivity for MUC6, diffuse positivity for CD10, weak positivity for Glypican 3 and negative staining for MUC2, MUC5AC, AFP and SALL4.
Gastric cancer with enteroblastic differentiation (GCED) was proposed as a disease with a very low incidence rate, the number of patients was small. Furthermore, the data were collected retrospectively in a single medical center, which may produce selection bias. In conclusion, GCED is rare, but has distinct clinicopathological features, especially in terms of high malignant potential and difficulty in preoperative diagnosis by biopsy specimens and prediction of submucosal invasion by endoscopic findings. It is necessary for endoscopists and pathologists to be aware of the clinicopathological features of such a rare and highly malignant type of cancer. In addition, when we detect specific histological findings for GCED with hematoxylin and eosin stain, immunohistochemical examination should be performed to make a precise diagnosis. However, there has been no report that evaluated a large number of cases. Further investigations are needed to elucidate the natural history of GCED by assessing the long-term outcome and establishing optimal treatment approaches for GCED.

COMMENTS

Background
Gastric cancer with enteroblastic differentiation (GCED) was proposed as a very rare variant of alpha-fetoprotein-producing gastric cancer (AFPGC). In previous reports, AFPGC was usually associated with a poor prognosis with a high incidence of lymphatic invasion, venous invasion, and synchronous and metachronous liver metastasis. Recently, with the advent and widespread use of endoscopic submucosal dissection (ESD), indications for endoscopic treatment of early stage gastric cancer have been expanding rapidly. Therefore, it is necessary for endoscopists to know the clinicopathological features of various histological types of early gastric cancer. However, the clinicopathological features and the optimal treatment approaches of GCED have not been well elucidated. In this study, we investigated clinicopathological features of early stage of GCED.

adenocarcinoma and GCED. In addition, the superficial mucosal layer was covered with a conventional tubular adenocarcinoma, and there were no findings of GCED components exposed to the superficial layer. Therefore, since we could only collect superficial mucosal layer tissue for the biopsy specimens, we felt that GCED could not be diagnosed by examination of biopsy specimens. The GCED component exists only in the deeper part of the mucosa to the submucosa by lymphatic and/or venous invasion but not in any other histological type of AFPGC (HGC and yolk sac type). As in previous reports, these findings suggested that GCED could be thought to develop from CGC and then gradually develop hepatoid features during the process of tumor invasion and proliferation. We considered that there is a possibility that early stage GCED represents the early developmental stage of AFPGC, which has various mixtures of histological types.

Endoscopically, we diagnose the depth of invasion according to endoscopic features of gastric cancers with deep submucosal invasion ($\geq 500 \mu m$ in depth), such as remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds. However, we could not anticipate the presence of deep submucosal invasion because none of these findings were revealed in our 6 GCED cases. The reason may be that there were few macroscopic changes in endoscopic morphology because the main submucosal invasive form of GCED depends on lymphatic and/or venous invasion and there were no severe stromal reactions.

In previous reports, AFPGC was usually associated with a poor prognosis with a high incidence of lymphatic invasion, venous invasion, and synchronous and metachronous liver metastasis. Hirasaki et al. studied 24 cases of AFP-producing early gastric cancer and reported that liver metastasis was seen in 2 cases (8.3%) and lymph node metastasis was seen in 18 of 24 cases (75.0%). From these results, they suggested that lymph node metastasis should be generally taken into consideration in AFPGC producing early gastric cancer even if lymph node swelling is not seen on diagnostic imaging and that such patients should be under close periodic observation. Furthermore, Adachi et al. studied 270 cases of AFPGC and reported that there were 61 patients who underwent curative gastrectomy for stage I or II AFPGC, and that 39 of those patients (64%) were alive during a median follow-up period of 27 mo. From these results, it is difficult to say that the prognosis was good. Although in this study the mean diameters of GCED and CGC were about the same, comparisons of M and SM invasive cancer, positive rates of lymphatic and venous invasion, and non-curative resection rates were significantly higher in GCED than CGC. Furthermore, when comparing only SM invasive cancer, the positive rate of venous invasion was significantly higher in GCED than CGC (100% vs 4.2%, $P < 0.01$). Although lymph node swelling cannot be seen on diagnostic imaging, lymph node metastasis occurred in 1 of 2 GCED cases who underwent additional surgery. In addition, although all of the 4 GCED cases for whom we could follow their complete progress were alive during the median follow-up period of 40 mo, 5 of 6 GCED cases (83.3%; 4 of 4 SM invasive cancer, 100%) had endoscopic non-curative resection because of deep submucosal invasion, lymphatic and/or venous invasion, and a positive margin. Therefore, we think that GCED, as well as AFPGC, may have a high incidence of liver and lymph node metastasis because of the high level of affinity to vessels and is associated with a poor prognosis in comparison with CGC. In this study, 2 of 5 cases who had endoscopic non-curative resection were followed up without additional surgery. One of the 5 cases had additional surgery and the remaining 2 were followed elsewhere. Although the 2 cases that we are following are alive without a recurrence (case 2: 42 mo, case 5: 38 mo), it is thought that close periodic observation is strictly required in such cases.

The present study had some limitations. Since GCED is a disease with a very low incidence rate, the number of patients was small. Furthermore, the data were collected retrospectively in a single medical center, which may produce selection bias.
This most remarkable point of this manuscript is the analysis of the influence of hepatocellular carcinoma and an unfavorable prognosis in the human fetal liver and silenced in the adult liver, but it is reexpressed in a hepatocellular carcinoma. SALL 4, it is an oncofetal protein that is expressed in the human fetal liver and placenta. It was discovered as a potential serological and histochemical marker whose expression is specific for hepatocellular carcinoma. SALL 4, it is an oncofetal protein that is expressed in the human fetal liver and silenced in the adult liver, but it is reexpressed in a subgroup of patients who have hepatocellular carcinoma and an unfavorable prognosis.

Applications
If the authors detect specific histological findings for GCED with hematoxylin and eosin stain, immunohistochemical examination, especially Glypican 3 should be performed to make a precise diagnosis. However, there has been no report that evaluated a large number of cases. Further investigations are needed to elucidate the natural history of GCED by assessing the long-term outcome and establishing optimal treatment approaches for GCED.

Terminology
ESD is a well established technique of endoscopic resection that allows for en bloc removal of GI epithelial lesions. Glypican 3, it is an oncofetal protein that is expressed in the human fetal liver and placenta. It was discovered as a potential serological and histochemical marker whose expression is specific for hepatocellular carcinoma. SALL 4, it is an oncofetal protein that is expressed in the human fetal liver and silenced in the adult liver, but it is reexpressed in a subgroup of patients who have hepatocellular carcinoma and an unfavorable prognosis.

Peer-review
This most remarkable point of this manuscript is the analysis of the influence of this rare type of tumor and its bad prognosis in comparison to the conventional one that justifies the research in this subtype.

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