Extremely well-differentiated adenocarcinoma of the stomach: Clinicopathological and immunohistochemical features

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Abstract

AIM: Minimal deviation carcinoma of the uterine cervix, otherwise known as extremely well-differentiated adenocarcinoma (EWDA), is characterized by its benign microscopic appearance in contrast to its aggressive behavior. In order to elucidate the clinicopathological features and biological behavior of the gastric counterpart of EWDA, we, using immunohistochemistry, analyzed nine lesions for the phenotypic expression, proliferative activity, and the expression of oncogene-associated products.

METHODS: Clinicopathological features, including pre-operative biopsy diagnosis, were reviewed. Using immunohistochemistry, Ki-67 labeling index and expression of p53 and c-erbB-2 protein in the gastric lesions were detected.

RESULT: Locations in the middle or upper third of the stomach and polypoid macroscopic features are characteristic of EWDA of the stomach. Although 4 of the 9 lesions showed only focal lymphatic or venous invasion, lymph node metastasis was not present and none of the patients died of the lesions (mean follow-up period, 56 mo). All 9 cases of EWDA could be classified into gastric phenotype (5 lesions) and intestinal phenotype (4 lesions). The former resembled gastric foveolar epithelium, mucous neck cells or pyloric glands, but their papillary structures were frequently elongated and the tumor cells and their nuclei were slightly larger and more hyperchromatic compared to normal epithelium. The latter resembled intestinal metaplasia with minimal nuclear atypia and irregular glands; two of these lesions demonstrated complete intestinal phenotype, while two demonstrated incomplete intestinal phenotype. Ki-67 labeling index was low and none of the cases revealed over-expression of p53 and c-erbB-2 protein.

CONCLUSION: Unlike minimal deviation carcinoma of the cervix, these findings suggest that EWDA of the stomach is a lesion of low-grade malignancy. This favorable biological behavior is supported by the data of a low Ki-67 labeling index and a lack of p53 or c-erbB-2 protein over-expression. Because of its resemblance to normal gastric mucosa or mucosa with intestinal metaplasia, EWDA is often misdiagnosed. To prevent the misdiagnosis of such lesions, the clinical and pathologic characteristics should be taken into consideration.

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Key words: Stomach neoplasms; Extremely well-differentiated adenocarcinoma; Ki-67; p53; c-erbB-2

INTRODUCTION

Silverberg and Hurt proposed the term “minimal deviation carcinoma” for extremely well-differentiated adenocarcinoma (EWDA) of the uterine cervix[1], which has a benign microscopic appearance yet shows an aggressive behavior[2,3]. This carcinoma is characterized by mucinous glands which resemble normal endocervical glands but invade the cervical stroma. Several similar cases of adenocarcinomas which show deceptive benign appearance have been reported in the stomach[4,5]. In those reports, the difficulty with histological diagnosis based on biopsy specimens is well discussed in detail; however, the biological behavior of the lesions still remains unclear.

Based on Lauren classification[6], gastric carcinomas
have been classified into two types, intestinal-type and diffuse-type. Following recent advances in mucin histochemistry and immunohistochemistry, it has been clarified that differentiated adenocarcinoma can be classified into two subtypes, these being gastric and intestinal phenotypes[14-20]. With regard to EWDA of the stomach, Endoh et al[21] reported eight cases of EWDA mimicking complete-type intestinal metaplasia, confirmed by phenotypic expression using immunohistochemical methods. Most reported cases of EWDA of the stomach seem to be intestinal-type carcinomas, resembling complete or incomplete intestinal metaplasia[21-27]. In addition, we have encountered a few reports of cases of EWDA mimicking normal gastric mucosa, where the cases were considered to be lesions of the gastric phenotype. However, in these cases, there was very little objective investigation of the phenotypic expression.

In order to elucidate the characteristics of EWDA including its biological behavior, we describe herein the clinicopathological features of nine cases, including phenotypic expression, proliferative activity and expression of some oncogene-associated products.

**MATERIALS AND METHODS**

**Patients**

EWDA is defined as neoplastic lesions composed of highly differentiated neoplastic epithelium which mimics the normal gastric mucosa or intestinal metaplastic mucosa with mild nuclear atypia, but has the ability to invade the gastric wall. We retrospectively reviewed 3106 cases from our old consecutive files that had been diagnosed as well-differentiated adenocarcinoma of the stomach, and found three (0.1%) cases of EWDA. Other 6 collected cases of EWDA were added, making a total of 9 cases for this study. One of the reported cases[7] was included in this study. Although we encountered some similar lesions restricted to the mucosa, these were excluded because of difficulty in diagnosing them as malignant.

The clinicopathological findings were principally based on the General Rules for Gastric Cancer Study as outlined by the Japanese Research Society for Gastric Cancer[21]. Eight specimens were obtained by surgery, and one was endoscopically resected. The resected specimens were fixed in 100 mL/L buffered formalin. The early lesions were cut only once through their center. The sections were then embedded in paraffin. Then 4-μm thick sections were routinely stained with hematoxylin and counterstained with methyl-green or hematoxylin. The negative controls consisted of substituting mouse normal serum for the primary antibodies.

**Evaluation**

The positivities of human gastric mucin (HGM), MUC6, MUC2 and CD10 were estimated as being significantly positive when more than 10% of the area was positive-stained. According to the combination of their expression, phenotypes were classified into four types: gastric type (G-type), intestinal-type (I-type), complete intestinal type (Comp. I-type), and unclassified type (Table 1)[29].

The Ki-67 (MIB-1, dilution 1:200; Nichirei, Tokyo) labeling index (LI) was defined as the percentage of MIB-1-positive nuclei, and was evaluated in the invasive areas. The MIB-1 LI was determined by counting at least 1 000 nuclei in the selected fields at x400 magnification. The p53 immunoreactivity was defined as positive when distinct nuclear staining was recognized in at least 10% of the cells, since most of the previously published studies employed this as the cut-off level. Cases with less than 10% positive cells were regarded as negative. c-erbB-2 was regarded as positive when there was membranous staining in more than 10% of the area of the tumor.

**RESULTS**

**Histologic findings and phenotypic expression**

All the EWDA had invaded the submucosa or even deeper; four were restricted to the submucosa, two had invaded the muscularis propria, and three had reached the subserosa beyond the muscularis propria. The EWDAs were classified into gastric phenotype (HGM+ or MUC6+/MUC2-/CD10-) containing 5 cases and

| Table 1 Phenotypic classification by immunohistochemical stains |
|---------------------------------------------------------------|
| **Human gastric mucin or MUC6**                              |
| (+) C - type                                                 |
| (-) D10                                                      |
| (+) MUC2                                                     |
| (-) U - type                                                 |
| (+) G - type                                                 |

C: complete intestinal, I: incomplete intestinal, G: gastric, U: unclassified.
An early lesion of extremely well-differentiated adenocarcinoma of the stomach, gastric-type (case 4). A: Macroscopic view showing a polypoid lesion with an irregular surface; B: cancer invasion of the whole thickness of the gastric wall (low-power view); C: carcinoma mimicking the normal gastric foveolar epithelium with basally located small nuclei (hyperchromatic nuclei) and abundant mucin; D: papillary projections occasionally seen in the carcinomatous glands; E: diffuse positive staining of human gastric mucin in carcinomatous glands; and F: focally positive staining of MUC6 in carcinomatous glands.

Figure 2 An early lesion of extremely well-differentiated adenocarcinoma of the stomach, complete intestinal-type (case 8). A: Macroscopic view showing a shallow depressed lesion with an irregular margin; B: carcinoma invasion to the submucosal layer (low-power view); C and D: carcinoma mimicking the intestinal metaplasia of complete-type with basally located small nuclei, eosinophilic cytoplasm and scattered goblet cells. Note the irregular arrangement of glands and intraluminal debris; E: CD10 positivity of carcinomatous glands along the luminal surfaces; and F: MUC2 positivity of scattered goblet cells.

Figure 3 An advanced lesion of extremely well-differentiated adenocarcinoma of the stomach, complete intestinal-type (case 9). A: Macroscopic view showing a polypoid mass with an irregular surface, but unclear margin; B: cancer invasion of the whole thickness of the gastric wall (low-power view); C: carcinomatous gland infiltrating into the submucosa; D: carcinoma mimicking the intestinal metaplasia of complete-type with basally located small nuclei, eosinophilic cytoplasm and scattered goblet cells.

Intestinal phenotype containing 4 cases. The intestinal phenotype cases were further classified into complete intestinal phenotype (HGM- / MUC6- / MUC2 + / CD10+) and incomplete intestinal phenotype (HGM- / MUC6- / MUC2 + / CD10+), each phenotype contained 2 cases. With regard to MUC6 expression which indicates differentiation to the pyloric glands, MUC6 expression was only detected in 2 of 5 cases of the gastric phenotype.

The five lesions classified as gastric phenotype were composed of well-differentiated epithelium mimicking foveolar epithelium, mucous neck cells or pyloric glands with abundant clear cytoplasm and basally situated nuclei. With careful observation, the nuclei were seen to be slightly larger than those of normal gastric mucosa, and to be markedly hyperchromatic. The superficial area tended to resemble the foveolar epithelium while the deep area tended to resemble mucous neck cells or pyloric glands. Two lesions mainly showed remarkable papillary proliferation. The epithelium was lined with a single layer of columnar cells with abundant clear cytoplasm with basally situated nuclei. The glands in this phenotype showed intraluminal papillary projections with or without a fibrous core. In the invasive area, one of five revealed marked desmoplastic reaction, however, other four revealed only slight desmoplastic reaction. One of the cases of gastric-type EWDA is shown in Figure 1.

The four lesions classified as intestinal phenotype were composed of intestinal-type glands with various amounts of goblet cells and Paneth cells, focally showing an irregular shape. Brush border-like structures were occasionally seen, and were confirmed by CD10 staining in the two cases classified as complete intestinal phenotype. We found difficulty in diagnosing these lesions as neoplastic in the mucosa because their glands were somewhat regular in shape and their cytologic atypia was minimal. However, their glands were of varying sizes and showed irregular branching in the deep portion of the mucosa and the submucosa. The glands in the submucosa or proper muscle layer were surrounded by an acute, chronic inflammatory infiltrate with lymphoid follicles. Occasionally, cystically dilated gland was seen in the submucosa, and mucous which had partially leaked out into the stroma owing to destruction of the glands, was seen in these three lesions. In the invasive area, all the four cases revealed marked desmoplastic reaction. Two cases of intestinal-type EWDA, early and advanced, are shown in Figures 2 and 3.

Regarding the background mucosa of the tumors, the surrounding mucosa could not be examined in one gastric phenotypic lesion because the lesion had been endoscopically resected. In another gastric phenotypic lesion, no intestinal metaplasia was seen. As for the other seven cases, various degrees of intestinal metaplasia were
seen in the surrounding mucosa of both the gastric and intestinal phenotypes.

**Patient characteristics**
The clinicopathological findings of the nine patients with EWDA of the stomach are summarized in Table 2. The patients included eight men and one woman with ages ranging from 45 to 81 (average 62) years. There were no patients who were diagnosed as Peutz-Jeghers syndrome. None of the patients died or suffered recurrence during the follow-up periods which ranged from 5 to 136 (average, 56) mo.

**Macroscopic findings**
The tumors had a maximum diameter of 1.5 to 8 (average, 3.6) cm. Of the nine lesions, three tumors were located in the upper third of the stomach, the remaining six were located in the middle third. No lesions were present in the lower third. Among the four early lesions (restricted to the submucosa), two lesions were of superficial depressed (Type 0-IIc) type or protruding (type 0-I) type. All the advanced lesions (invading the muscularis mucosa and/or the subserosa) were of polyloid type (Type I).

**Pre-operative biopsy**
Pre-operative biopsy specimens could be evaluated only in seven cases because of unavailability of specimens in two cases. Two of the seven cases were diagnosed as benign lesions, and the remaining five were initially suspected as being carcinomas, although there was difficulty in distinguishing whether they were neoplastic or regenerative lesions. Only one lesion could be finally diagnosed as a definite carcinoma through repeated biopsy (Case 9).

**Ki-67, p53 and c-erbB-2 expressions**
None of the cases of EWDA revealed over-expression of p53 or c-erbB-2. Regarding the proliferating activity, the mean value of Ki-67 LI of the EWDA was 8.7% (range, 0.5%-23.9%).

**DISCUSSION**
Gastric carcinomas, based on Lauren classification, have been divided into two histologic types by standard hematoxylin and eosin (H&E) staining, such as

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**Table 2 Clinicopathological data**

| Case | Age | Sex | Loc | Size | Macro | Depth | ly | v | LN | Prognosis | Biopsy |
|------|-----|-----|-----|------|-------|-------|----|---|----|-----------|--------|
| 1    | 81  | m   | M   | 5.5  | 0-I   | sm    | (+) | (-) | NA | 5 mo, alive | benign |
| 2    | 51  | m   | U   | 2.5  | 0-IIa | sm    | (-) | (-) | NA | 23 mo, alive | NA     |
| 3    | 63  | m   | M   | 8    | 0-I   | ss    | (-) | (-) | NA | 66 mo, alive | benign |
| 4    | 76  | m   | U   | 3.5  | 0-I   | ss    | (-) | (+) | NA | 30 mo, alive | Ca, susp |
| 5    | 57  | m   | U   | 5    | 0-I   | ss    | (+) | (-) | NA | 48 mo, alive | NA     |

**Intestinal phenotype (incomplete intestinal-type)**

| 6    | 65  | f   | M   | 1.5  | 0-IIa | sm    | (+) | (-) | (-) | 38 mo, alive | Ca, susp |
| 7    | 45  | m   | M   | 2.4  | 1     | mp    | (-) | (-) | NA | 129 mo, alive | Ca, susp |

**Table 3 Previously reported cases of gastric EWDA**

| Case | Author | Age | Sex | Macro | Location | Size | Depth | ly | v | n | Prognosis | Phenotype | Biopsy |
|------|--------|-----|-----|-------|----------|------|-------|----|---|---|-----------|-----------|--------|
| 1    | Araki  | 50  | m   | I    | M        | 45   | ss    | 1  | 0 | 0 | ?         | Incomp-I  | benign |
| 2    | Satoh  | 65  | m   | I    | U        | 40   | mp    | 0  | 0 | 0 | ?         | Comp-I    | benign |
| 3    | Yososaka| 53  | m   | I    | M        | 80   | mp    | 2  | 0 | 1 | ?         | Comp-I    | benign |
| 4    | Matsunaga| 42  | m   | 0-I | L        | 45   | sm    | 2  | 0 | 0 | ?         | reg. Atypia|         |
| 5    | Kobayashi| 55  | m   | I    | M        | 20   | ss    | 0  | 0 | 0 | ?         | Comp-I    | benign |
| 6    | Endoh  | 60  | f   | 0-IIb+IIc| M      | 10   | sm    | 0  | 0 | 0 | ?         | Comp-I    | Ca       |
| 7    | Endoh  | 68  | f   | 0-IIc+IIb| M      | 20   | sm    | 0  | 0 | 0 | ?         | Comp-I    | Ca       |
| 8    | Endoh  | 70  | m   | 0-IIb| M        | 27   | sm    | 0  | 0 | 0 | ?         | Comp-I    | NA       |
| 9    | Endoh  | 62  | f   | 0-IIc+IIa| M      | 15   | sm    | 0  | 0 | 0 | ?         | Comp-I    | NA       |
| 10   | Endoh  | 59  | m   | 0-IIa| M        | 15   | sm    | 0  | 0 | 0 | ?         | Comp-I    | Ca       |
| 11   | Endoh  | 74  | m   | 0-IIa+IIc| L      | 18   | sm    | 0  | 0 | 0 | ?         | Comp-I    | NA       |
| 12   | Endoh  | 70  | m   | 0-IIa+IIc| M      | 25   | sm    | 0  | 0 | 0 | ?         | Comp-I    | benign  |
| 13   | Endoh  | 65  | m   | I    | M        | 55   | se    | 0  | 0 | 0 | ?         | Comp-I    | benign  |
| 14   | Adachi | 54  | m   | 0-I | M        | 40   | sm    | ?  | 0 | 0 | ?         | ?         | benign  |
| 15   | Sato   | 50  | m   | 2   | M        | 48   | ss    | 2  | 0 | 0 | ?         | Mixed     | benign  |

Loc: location (U: upper third, M: middle third), Macro: macroscopic feature, Depth: depth of invasion (sm: submucosa, mp: muscularis propria, ss: subserosa), ly: lymphatic permeation, v: venous invasion, LN: lymph node metastasis, NA: not assessed, Ca: carcinoma, Ca, susp: carcinoma, suspected.
The histological features of EWDA with regard to pre-differential diagnosis of neoplastic or dysplastic lesions in is important to take it into consideration when making a attention. Although EWDA of the stomach is very rare, it two of our current seven cases. These highly differentiated negative in eight of 12 cases in previous reports and in prior to surgery. In fact, pre-operative biopsies were difficulties especially with regard to biopsy specimens cell atypia of these lesions result in frequent diagnostic epithelium. The high degree of differentiation and mild is more likely to be confused with intestinal metaplastic hyperplastic polyps, although some of them strikingly elongated. In addition, the individual cells and nuclei were obviously larger and their nuclei were more hyperchromatic than those in normal foveolar epithelium. Since the cellular atypism is minimal, it is important to compare their size and the amount of chromatin with that in the surrounding normal epithelium.

There have been no reports about the biological behavior of EWDA, although a low incidence of lymphovascular invasion and lymph node metastasis has been noted (Table 3). As for our cases, all the patients are currently alive. Three lesions revealed only focal venous or lymphatic invasion, but no lymph node metastasis was seen in our cases of EWDA. These findings suggest a favorable prognosis for EWDA of the stomach unlike the prognosis for minimal deviation adenocarcinoma of the uterine cervix, although it needs to be noted that our series was small with limited follow-up data. With regard to the correlation between phenotypes and clinicopathological features, there was no significant difference between the two except for tumor location. Three of the five EWDA's of gastric phenotype were located in upper third of the stomach, whereas all the EWDA's of intestinal phenotype were located in the middle third.

The proliferative compartment in normal gastric mucosa is known to be restricted to the middle layer of the mucosa. Several reports have indicated the relationship between a high Ki-67 LI and poor prognosis in cases of gastric carcinoma. In our present study, the Ki-67 LI was lower (average, 8.7%) compared with the previously reported data(from 41.8% to 47.1%) . A low Ki-67 LI (13%) in the submucosal invasive area has also been reported by Endoh et al, and this finding reflects the slow growth and reduced aggressiveness of EWDA of the stomach.

The reported prevalences of abnormal expression of p53 and c-erbB-2 protein have been shown to range from 47% to 60% and from 5.7% to 33.0%, respectively. It has been reported that the over-expression of p53 is a marker of poor prognosis in gastric carcinoma. Fortunately, none of the lesions of EWDA showed over-expression of p53 or c-erbB-2 in our study. It seems reasonable to regard these lesions as having a low-grade malignancy, but an ability to invade downward into the gastric wall, a finding which is supported by the data of low Ki-67 LI and no over-expression of p53 or c-erbB-2. In addition, these immunoreactivities of p53 and c-erbB-2 seemed to be useless for the diagnosis of EWDA.
In the practical diagnosis of a stomach biopsy, it is important to bear in mind the existence of extremely well-differentiated adenocarcinoma (EWDA) of both intestinal and gastric types.

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