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The Characteristics and Prognosis of Diffuse-Type Early Gastric Cancer Diagnosed during Health Check-Ups

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Background/Aims: Because of the poor prognosis of diffuse-type gastric cancer, early detection is important. We investigated the clinical characteristics and prognosis of diffuse-type early gastric cancer (EGC) diagnosed in subjects during health check-ups. **Methods:** Among 121,111 subjects who underwent gastroscopy during a routine health check-up, we identified 282 patients with 286 EGC lesions and reviewed their clinical and tumor-specific parameters. **Results:** Patients with diffuse-type EGC were younger, and 48.1% of them were female. Serum anti-*Helicobacter pylori* IgG (Hp-IgG) was positive in 90.7% of diffuse-type EGC patients (vs 75.9% of intestinal-type EGC, p=0.002), and the proportion of diffuse-type EGC cases increased significantly with increasing Hp-IgG serum titers (p<0.001). Diffuse-type EGC had pale discolorations on the tumor surface (26.4% vs 4.0% in intestinal-type EGC, p<0.001) and were often located in the middle third of the stomach. Submucosal invasion or regional nodal metastasis was observed more commonly in patients with diffuse-type EGC. However, during the median follow-up period of 50 months, 5-year disease-free survival rates did not differ between the groups. **Conclusions:** Diffuse-type EGC shows different clinical and endoscopic characteristics. Diffuse-type EGC is more closely associated with Hp-IgG seropositivity and a higher serum titer. Early detection results in excellent prognosis. **(Gut Liver 2017;11:807-812)**

Key Words: Stomach neoplasms; Diffuse-type; Early diagnosis; Prognosis; Endoscopy

INTRODUCTION

Gastric cancer (GC) is the most prevalent malignancy in Korea.[1] A nationwide health check-up program by the Korean Central Cancer Registry recommends biennial gastroscopy for individuals older than 40 years.[2,3] The prognosis of GC is improving because of early diagnosis of the condition with the screening program.

Histologically, GC is classified into intestinal and diffuse types.[4] Intestinal-type GC arises mostly from *Helicobacter pylori*-induced chronic gastritis through the intermediate stages of atrophic and metaplastic gastritis.[5] On the contrary, active inflammation of the gastric mucosa by *H. pylori* induces diffuse-type GC without passing through the premalignant lesions.[6,7] The obscure premalignant changes and active inflammation of the mucosa may lead to early-stage diffuse-type GC being missed during endoscopic examination.

Diffuse-type GC has a worse prognosis than intestinal-type GC because of the frequent nodal and distant metastasis in the former.[8-10] Thus, understanding the characteristics of diffuse-type GC at an early stage is essential to improve the detection and prognosis of the disease. In this study, we evaluated the clinical and endoscopic features of the patients with diffuse-type early gastric cancer (EGC) diagnosed in subjects undergoing health check-up, and compared the prognosis of these subjects to that of patients with intestinal-type EGC.

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MATERIALS AND METHODS

1. Patients and data collection

From a database of 121,111 subjects who underwent gastroscopy during health check-up between January 2008 and December 2013 at the Health Screening and Promotion Center of Asan Medical Center, we identified 358 patients who were diagnosed with gastric malignancies. Of these, 76 patients were excluded from the analysis owing to advanced-stage GC (n=48), cardia cancer (n=14), stump cancer (n=10), and lymphoma (n=4). Finally, 282 patients with non-cardia EGC were included in this study. All participants were voluntary, self-referred asymptomatic adults who completed a self-administered questionnaire that detailed their personal medical history, family history of GC, and lifestyle habits. Our screening protocol for GC is based on the Korean National Gastric Cancer Screening Program,[2] in which asymptomatic individuals older than 40 years of age who have an average risk for GC are recommended to undergo biennial gastroscopy.

This study was approved by the Institutional Review Board of the Asan Medical Center (2014-0455), which confirmed that it accorded with the Ethical Guidelines of the Declaration of Helsinki.

2. Endoscopic procedures

Gastroscopy was performed by specialized gastrointestinal endoscopists, who had received gastrointestinal fellowship training and board certification. A high-resolution electronic endoscope (GIF-Q260 or GIF-H260; Olympus Optical, Tokyo, Japan) was used for gastroscopy. Patients were sedated with intravenous midazolam (0.05 mg/kg), and their cardiorespiratory functions were monitored closely during the procedure. Endoscopic features such as lesion size, location, and macroscopic types were recorded for any suspicious lesions. Presence of abnormal fold convergence, spontaneous bleeding at foci, mucosal defect (erosion or ulceration), and color change on the surface of lesions was noted. The macroscopic features of the tumors were classified into three major types: elevated (I and IIa), flat (IIb), or depressed (IIc and III).[11,12] The extension of mucosal atrophy was categorized as closed or open type, according to Kimura and Takemoto classification.[13]

3. Histological classification

Tumors were classified as diffuse or intestinal type on the basis of the Lauren criteria.[4] Any tumor showing more than two histologic types was classified into one type according to the predominant histologic pattern. According to glandular differentiation, tumors were categorized into differentiated or undifferentiated type, based on the World Health Organization criteria.[14] EGC is defined as GC confined to the mucosa or submucosa, irrespective of regional lymph node metastasis.[11] Endoscopic resection was performed in cases where the differentiated-type EGC was confined to the mucosa, was <20 mm in diameter, and did not show nodal enlargement on abdominal computed tomography.[15,16]

4. Serum anti-*H. pylori* IgG antibody

Serological positivity to anti-*H. pylori* IgG (Hp-IgG) was determined using the *H. pylori* IgG immunoassay system (Immulite 2000; Siemens Healthcare Diagnostics Products Ltd., Llanberis, Gwynedd, UK). The calibration range of this immunoassay is 0.4 to 8.0 U/mL, and the serum Hp-IgG titer is reported as follows: negative, 0 to 0.8 U/mL; equivocal, 0.9 to 1.0 U/mL; positive, 1.1 to 7.9 U/mL; and high-positive, values higher than the upper calibration limit. In this study, patients with Hp-IgG values ≤1.0 U/mL were considered seronegative for *H. pylori* infection because most of those with equivocal level of Hp-IgG titer had no evidence of current *H. pylori* infection.[17] We divided patients in the positive group into two subgroups, the low-positive (1.1 to 3.6 U/mL) and the mid-positive (3.7 to 7.9 U/mL) groups, in which the cutoff value was determined to ensure that the same number of patients were included in each subgroup.

5. Statistical analysis

The baseline continuous and categorical variables are presented as the mean±standard deviation and number with percentage, respectively. Group comparisons of the continuous variables were performed using Student t-test, and the categorical variables were compared using the Pearson chi-square test. The correlations between the Hp-IgG titer distribution and proportion of diffuse-type EGC were analyzed using linear-by-linear association. The 5-year disease-free survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test. A p-values less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Clinical characteristics of patients with intestinal- and diffuse-type EGC

Among the 282 patients with EGC, intestinal-type EGC was diagnosed in 176 lesions in 174 patients (61.7%) and diffuse-type EGC was diagnosed in 110 lesions in 108 patients (38.3%). Patients with diffuse-type EGC were younger than those with intestinal-type EGC, and 48.1% of them were female (Table 1). All six patients with EGC who were aged less than 40 years were diagnosed with diffuse-type EGC. More patients with intestinal-type EGC reported histories of smoking and the presence of GC in first-degree relatives.

Serum Hp-IgG was found to be positive in 90.7% of patients with diffuse-type EGC (vs 75.9% of patients with intestinal-type EGC; p=0.002). A high-positive titer of serum Hp-IgG (≥8.0 U/mL) was reported in 24.1% of patients with diffuse-type EGC

Table 1. Clinical Characteristics of Patients with Early Gastric Cancer

	Total (n=282)	Intestinal-type (n=174)	Diffuse-type (n=108)	p-value
Age, yr	56.8±9.8	59.1±9.2	53.1±9.6	<0.001
<40	6 (2.1)	0	6 (5.6)	
40–59	174 (61.7)	99 (56.9)	75 (69.4)	
≥60	102 (36.2)	75 (43.1)	27 (25.0)	
Female sex	84 (29.8)	32 (18.4)	52 (48.1)	<0.001
Family history of gastric cancer*	59 (20.9)	46 (26.4)	13 (12.0)	0.004
Alcohol consumption	114 (40.4)	74 (42.5)	40 (37.1)	0.463
Smoker	170 (60.3)	121 (69.6)	49 (45.4)	<0.001
Anti-*H. pylori* IgG positivity	230 (81.6)	132 (75.9)	98 (90.7)	0.002
Serum anti-*H. pylori* IgG titer, U/mL				<0.001
Negative (0–1.0)†	52 (18.4)	42 (24.1)	10 (9.2)	
Low-positive (1.1–3.6)	98 (34.8)	63 (36.2)	35 (32.4)	
Mid-positive (3.7–7.9)	92 (32.6)	55 (31.6)	37 (34.3)	
High-positive (≥8.0)	40 (14.2)	14 (8.1)	26 (24.1)	
First screening endoscopy	84 (29.8)	52 (29.9)	32 (29.6)	0.964
Screening interval, mo	23.8±20.5	25.9±23.2	20.4±15.1	0.066
Treatment				<0.001
Endoscopic resection	135 (47.9)	127 (73.0)	8 (7.4)	
Surgical resection	147 (52.1)	47 (27.0)	100 (92.6)	

Data are presented as mean±SD or number (%).
*First-degree relatives; †Including 11 cases with equivocal serum anti-*H. pylori* IgG titers.

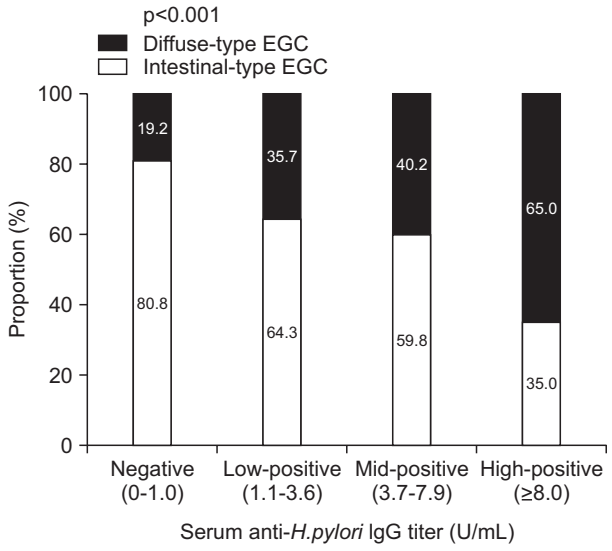

Fig. 1. The proportions of diffuse-type early gastric cancer (EGC) according to serum anti-*Helicobacter pylori* IgG titers. The proportion of diffuse-type EGC cases increased significantly with serum anti-*H. pylori* IgG titers (p-value by linear-by-linear association).

and 8.1% of patients with intestinal-type EGC. The proportion of diffuse-type EGC increased significantly with an increasing Hp-IgG serum titer (p<0.001) (Fig. 1); 65.0% of the patients with a high-positive Hp-IgG titer were diagnosed with diffuse-type EGC.

There were no differences in the proportions of patients who underwent their first-time screening gastroscopy and in the time interval from the latest gastroscopy. Endoscopic resection was performed in 73.0% of patients with intestinal-type EGC, whereas surgical resection was performed in 92.6% of patients with diffuse-type EGC.

2. Comparison of endoscopic features

Diffuse-type EGC mostly consisted of flat or depressed lesions (90.0%) with an ill-defined border (81.8%). Intestinal-type EGC was often found in the lower third of the stomach (72.2%), whereas in 56.4% of the patients, diffuse-type EGC was located in the middle third of the stomach. The proportion of tumors with pale discoloration on the surface was significantly different between patients with diffuse-type and intestinal-type EGC (26.4% and 4.0%, respectively; p<0.001). Open-type atrophic gastritis in the surrounding mucosa was observed in 69.5% of patients with intestinal-type EGC (vs 51.9% of patients with diffuse-type EGC; p=0.003). Table 2 compares the endoscopic features of intestinal- and diffuse-type EGCs.

3. Pathologic features and prognosis

The mean tumor size was 17.7±14.9 mm in intestinal-type EGC and 25.3±16.4 mm in diffuse-type EGC (p<0.001). Submucosal invasion or regional nodal metastasis was more common in diffuse-type EGC (Table 3).

Table 2. Endoscopic Features of Intestinal- and Diffuse-Type Early Gastric Cancer

	Intestinal-type (n=176)	Diffuse-type (n=110)	p-value
Tumor size, mm	14.4±11.6	20.8±15.6	<0.001
Tumor location			<0.001
Lower third	127 (72.2)	38 (34.5)	
Middle third	40 (22.7)	62 (56.4)	
Upper third	9 (5.1)	10 (9.1)	
Macroscopic feature			<0.001
Elevated	64 (36.4)	11 (10.0)	
Flat	44 (25.0)	53 (48.2)	
Depressed	68 (38.6)	46 (41.8)	
Tumor border, ill-defined	73 (41.5)	90 (81.8)	<0.001
Pale discoloration on tumor surface	7 (4.0)	29 (26.4)	<0.001
Converging folds	9 (5.1)	17 (15.5)	0.003
Spontaneous tumor bleeding	39 (22.2)	26 (23.6)	0.772
Mucosal defect	76 (43.2)	39 (35.5)	0.195

Data are presented as mean±SD or number (%).

Table 3. Pathologic Features of Intestinal- and Diffuse-Type Early Gastric Cancer

	Intestinal-type (n=176)	Diffuse-type (n=110)	p-value
Tumor size, mm	17.7±14.9	25.3±16.4	<0.001
Glandular differentiation			<0.001
Differentiated	166 (94.3)	7 (6.4)	
Undifferentiated	10 (5.7)	103 (93.6)	
Depth of invasion			0.002
Mucosa	157 (89.2)	83 (71.8)	
Submucosa	19 (10.8)	27 (24.5)	
Lymphovascular invasion	9 (5.1)	8 (7.3)	0.452
Metastatic regional lymph node	2 (1.1)	8 (7.3)	0.006
Perineural invasion	1 (0.6)	5 (4.5)	0.022

Data are presented as mean±SD or number (%).

No patients died during the median follow-up period of 50 months (range, 15 to 91 months). Five cases of tumor recurrence were reported after curative resection: Four cases of metachronous recurrence and one case of regional metastasis after surgery in patients with intestinal-type EGC. The overall 5-year disease-free survival rate was 98.2% (Fig. 2). The 5-year disease-free survival rates did not differ between patients with intestinal-type EGC and diffuse-type EGC (97.1% and 100%, respectively; p=0.079).

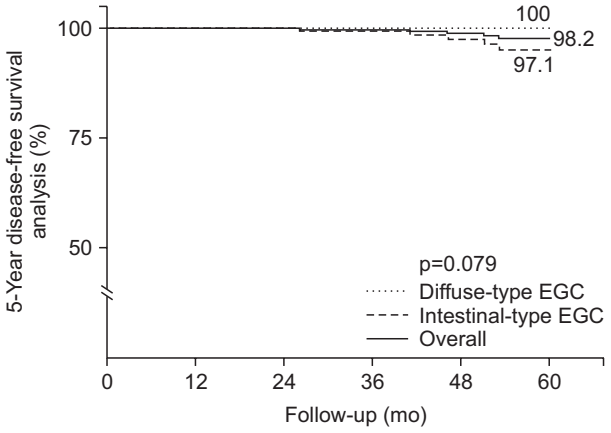

Fig. 2. Kaplan-Meier curves for the 5-year disease-free survival analysis. The 5-year disease-free survival rate was 98.2% in all patients with early gastric cancer (EGC), 97.1% in patients with intestinal-type EGC, and 100% in patients with diffuse-type EGC (p=0.079).

DISCUSSION

The current study showed that patients with diffuse-type EGC diagnosed during health check-ups were closely associated with younger age, female sex, and Hp-IgG seropositivity. In addition, diffuse-type EGC was found more often in those with a higher

serum Hp-IgG titer. When diagnosed at an early stage, the prognosis of diffuse-type EGC is excellent.

Diffuse-type EGC was observed more often in younger and female patients. In addition, 90.7% of patients with diffuse-type EGC showed positive serum Hp-IgG test results. The relatively lower positive rate of serum Hp-IgG (75.9%) in patients with intestinal-type EGC can be explained by the disappearance of *H. pylori* from the atrophic and metaplastic gastric mucosa with the progression of *H. pylori* infection.[18] In a study that reported the characteristics of GC according to *H. pylori* infection status, GC patients with past *H. pylori* infection were older and predominantly male, compared with the patients with current infection.[19] In terms of Lauren's histological classification, the proportion of diffuse-type GC was much higher in patients with GC who were currently infected with *H. pylori* than in those infected in the past. Moreover, patients with a serologic evidence of past infection had a higher proportion of diffuse-type GC compared with patients with a histologic past-infection (38.2% vs 19.8%, respectively). In that study, *H. pylori* test was positive in 87.2% of patients with GC, and seronegative past infection was reported in 10.5% of the patients.

In addition to the close association between diffuse-type EGC and Hp-IgG seropositivity, the proportion of diffuse-type EGC increased significantly with an increasing serum Hp-IgG titer. A previous study reported that a higher Hp-IgG titer was associated with a risk of diffuse-type GC.[20] In an analysis of patients with *H. pylori*-infected non-atrophic gastritis, the incidence of GC was significantly higher in a group of patients with a high Hp-IgG titer, and 80% of the cancers that developed in the high-titer group demonstrated diffuse-type histology.[7,21] In another study, the risk of diffuse-type GC was the highest in patients with high Hp-IgG titer without mucosal atrophy.[22] Considering that serum Hp-IgG titer was positively associated with the severity of histological inflammation,[23,24] some investigators speculated that the high inflammatory response to *H. pylori* infection increases the risk of developing diffuse-type GC in the absence of premalignant lesions.[25] They suggested careful follow-up with endoscopy at regular intervals in such subjects with a high-positive Hp-IgG titer.

On endoscopy, 26.4% of the cases of diffuse-type EGC showed pale discoloration on tumor surface. Diffuse-type tumors tend to infiltrate laterally without exposure to the mucosal surface and have a reduced subepithelial capillary network.[26-28] Pale discoloration on the tumor surface may be used as an endoscopic predictor for diffuse-type GC prior to resection.[29] Additionally, 65.5% of the tumors in diffuse-type EGC were located in the corpus part of the stomach (vs 27.8% in intestinal-type GC). Previous study showed that lesions located in the corpus could be missed easily and 70% of interval GC was undifferentiated-type histology.[30] Therefore, endoscopic examination should be performed carefully in this region, because early detection of tumors could be hampered by the gastric folds and oblique endoscopic view.

Diffuse-type GCs show an aggressive biological behavior and poor prognosis. In a previous report, patients with signet ring cell carcinoma and poorly differentiated GC in advanced stages demonstrated significantly lower 10-year overall survival rates than the survival rates of patients with advanced differentiated GC.[31] However, the 10-year overall survivals were better in patients with early signet ring cell and poorly differentiated carcinomas than in those with differentiated carcinomas (95%, 89%, and 84%, respectively). The 10-year overall survival of patients with mucosa-confined EGC was 93.4% for patients with intestinal-type EGC and 90.7% for those with diffuse-type GC.[32] The 10-year recurrence-free survival rate of patients with intestinal-type and diffuse-type EGC was 91.4% and 92.9%, respectively. In our study, 71.8% of diffuse-type EGCs were mucosa-confined cancers. The 5-year disease-free survival of patients with diffuse-type EGC was comparable to that of patients with intestinal-type EGC. The excellent prognosis of our patients may also be attributed to the endoscopic screening at regular intervals. During our study period, 88.2% of patients with GC were diagnosed as having EGC, and interval endoscopy was performed in 70.2% of the patients with EGC. The mean screening interval was 25.9 months in patients with intestinal-type EGC and 20.4 months in patients with diffuse-type EGC. As previously reported, endoscopic screening was associated with a significant increase in the detection of EGC and improvement in the chance of 5-year survival.[33,34]

In conclusion, diffuse-type EGC diagnosed in subjects during health check-ups was more closely associated with *H. pylori* seropositivity and found more often in those with a high-positive Hp-IgG serum titer. This type of tumor may present with pale discoloration in the middle third of the stomach in the absence of surrounding mucosal atrophy. The clinical and endoscopic characteristics of diffuse-type EGC may help in the early detection of the tumors, consequently leading to a good prognosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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