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Clinical and Endoscopic Features of Undifferentiated Gastric Cancer in Patients with Severe Atrophic Gastritis

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Abstract

Objective Differentiated gastric cancer generally develops in the atrophic gastric mucosa, although undifferentiated cancer is sometimes encountered in patients with severe atrophic gastritis. We characterized the endoscopic features of undifferentiated gastric cancer in patients with severe atrophic gastritis.

Methods Stage IA early gastric cancer was diagnosed in 501 patients who were admitted to our hospital between April 2003 and March 2012. The endoscopic and pathological findings were compared among 29 patients with undifferentiated cancer and severe atrophic gastritis, 104 patients with undifferentiated cancer and mild/moderate atrophic gastritis and 223 patients with well-differentiated cancer and severe atrophic gastritis. Endoscopic atrophic gastritis was classified according to the Kimura-Takemoto classification as no gastritis, C-1 and C-2 (mild), C-3 and O-1 (moderate) or O-2 and O-3 (severe).

Results The tumors were larger and showed deeper mural invasion in the patients with undifferentiated cancer and severe atrophic gastritis than in those with well-differentiated cancer and severe gastritis or undifferentiated cancer and mild/moderate gastritis. On endoscopy, undifferentiated cancer associated with severe gastritis was often red in color.

Conclusion It is often difficult to diagnose early undifferentiated gastric cancer, especially in patients with severe atrophic gastritis. The present study characterized the important endoscopic features of such tumors.

Key words: atrophic gastritis, endoscopy, gastric cancer, undifferentiated type, *Helicobacter pylori*

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Introduction

Although the mortality rate of gastric cancer has recently fallen in Japan, more than 100,000 new cases of this tumor are diagnosed annually. In 2010, the registered number of new patients with gastric cancer was 125,730, making it the most common malignancy in Japan (1). Since the leading cause of gastric cancer is chronic gastritis associated with infection with *Helicobacter pylori*, *H. pylori* eradication therapy has been actively promoted. However, the risk of gastric cancer still exists even after the eradication of *H. pylori*, suggesting that early detection and obtaining an accurate diagnosis of the disease on endoscopy remain important clinical steps in terms of the overall outcome.

Gastric cancer is histopathologically classified into well-differentiated and undifferentiated tumors, with both types being induced by cellular injury associated with *H. pylori* infection or genetic changes. Well-differentiated gastric cancer usually arises after the onset of progressive gastric mucosal atrophy and/or intestinal metaplasia due to chronic *H. pylori* infection. In contrast, undifferentiated cancer often arises from the gastric mucosa without any noticeable atrophic changes and can be more difficult to diagnose at an early stage, since there is no obvious precancerous state. Tumors detected on diagnostic endoscopy are usually assumed to be well differentiated with the simultaneous presence of background atrophic changes in the gastric mucosa, whereas these lesions are considered undifferentiated in the absence of such atrophic changes. However, clinical experience shows that undifferentiated cancers can arise even in the presence of atrophic gastritis.

In the present study, we evaluated the characteristics of background gastric mucosal atrophy in patients with Stage

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Table 1. Clinicopathological Features of 501 Patients with Stage IA Early Gastric Cancer.

Gender (males/females)	363/138
Age, years (mean±SD)	67.8±10.4
Treatment: Surgical/Endoscopic	260/241
Pathological findings	
Location: U/M/L	48/276/177
Macroscopic appearance: elevated (0-I, 0-IIa)/depressed (0-IIb, 0-IIc, 0-III) lesion	117/384
Histopathology	
Well-differentiated: pap/tub1/tub2	6/277/67
Undifferentiated: por1/por2/sig/muc	12/78/59/2
Size (mean±SD): major axis (mm)/minor axis (mm)	26.5±21.4/18.6±15.3
Depth: mucosa/submucosa	346/155
Ulceration: yes/no	158/343
Lymphatic invasion: yes/no	71/430
Vascular invasion: yes/no	19/482
Endoscopic findings	
Atrophic gastritis: mild/moderate/severe/unknown	50/178/252/21
Color of the lesion: faded/reddish	129/372
H. pylori infection: +/-/post eradication/unknown	296/49/9/147

IA undifferentiated gastric cancer who were diagnosed and treated at our hospital. We also compared Stage IA undifferentiated and well-differentiated gastric cancers in order to identify the characteristics of undifferentiated cancer associated with severe atrophic gastritis.

Materials and Methods

Patients

This study was conducted among 501 patients who underwent resection of early gastric cancer between April 2003 and March 2012 at the Institute of Gastroenterology of Tokyo Women's Medical University. The final diagnosis in all patients was Stage IA gastric cancer, according to the "Japanese Classification of Gastric Carcinoma (14th edition)." In this classification, well-differentiated cancer includes papillary adenocarcinoma (pap) and tubular adenocarcinoma (tub1, tub2), while undifferentiated cancer includes poorly-differentiated cancer (por1, por2), signet ring cell carcinoma (sig) and mucinous carcinoma (muc) (Table 1). The patients were divided into those with undifferentiated cancer (n=151) and well-differentiated cancer (n=350). Endoscopic atrophic gastritis was classified according to the Kimura-Takemoto classification as no gastritis, C-1 and C-2 (mild), C-3 and O-1 (moderate) or O-2 and O-3 (severe).

Data analysis

We reviewed the endoscopic findings obtained at the time of diagnosis. We then compared the severity of endoscopic atrophic gastritis between the patients with well-differentiated cancer and those with undifferentiated cancer and compared the scores for the endoscopic findings [e.g., scores for atrophy, intestinal metaplasia, enlarged folds, nodularity and diffuse redness] based on the "Scores for endoscopic findings taking the risk of gastric cancer into consideration" in the "Kyoto classification of gastritis" (Kyoto classification).

Of the 501 patients, 29 patients had undifferentiated gastric cancer with a background of endoscopically severe atrophic gastritis (undifferentiated+severe atrophy group) and 104 patients had undifferentiated cancer with mild or moderate atrophic gastritis (undifferentiated+non-severe atrophy group). After conducting a histopathological examination of the surgically resected specimens, the following items were compared between the two groups: age, gender, treatment, tumor location, macroscopic appearance, size, histopathology, depth of invasion, existence of ulcer-in-cancer, vascular invasion, lesion color on preoperative endoscopy, *H. pylori* infection detected based on measurements of antibodies in urine samples and the scores for endoscopic findings determined based on the Kyoto classification.

The same comparisons were also performed between the undifferentiated+severe atrophy group (n=29) and well-differentiated+severe atrophy group (well-differentiated cancer with a background of endoscopic severe atrophic gastritis n=223).

Statistical analysis and ethical considerations

The results are expressed as the mean ± standard deviation (SD). Comparisons of data between two groups were performed using the chi-square test and Mann-Whitney test. The Kruskal-Wallis test was used for comparisons of data among four groups. A p value of less than 0.05 denoted the presence of a statistically significant difference. All analyses were conducted using the Statistical Package for Social Sciences, version 13.0J (SPSS Inc., Tokyo, Japan).

Results

Among the 501 patients, the severity of atrophic gastritis could be evaluated in 481 patients (133 subjects with undifferentiated cancer and 348 subjects with well-differentiated cancer) and the scores for the endoscopic findings based on the Kyoto classification could be evaluated in 379 patients (98 subjects with undifferentiated cancer and 281 subjects with well-differentiated cancer). The findings are shown in Table 2. With regard to the grade of atrophy, the number of

Table 2. Comparison of Grade of Atrophy Based on "Kimura-Takemoto Classification" and Endoscopic Findings Based on "Kyoto Classification" between Well-differentiated Type and Undifferentiated Type.

	Undifferentiated type	Well-differentiated type	p value*
Grade of atrophy			<0.001
n	133	348	
Mild	28 (21.1%)	23 (6.6%)	
Moderate	76 (57.1%)	102 (29.3%)	
Severe	29 (21.8%)	223 (64.1%)	
Endoscopic findings			
n	98	281	
Atrophy			p<0.01
Score 0	3 (3.1%)	0 (0.0%)	
Score 1	54 (55.1%)	40 (14.2%)	
Score 2	41 (41.8%)	241 (85.8%)	
Intestinal metaplasia			n.s
Score 0	59 (60.2%)	130 (46.3%)	
Score 1	20 (20.4%)	73 (26.0%)	
Score 2	19 (19.4%)	78 (27.8%)	
Enlarged fold			p<0.01
Score 0	71 (72.4%)	264 (94.0%)	
Score 1	27 (27.6%)	17 (6.0%)	
Nodularity			p<0.05
Score 0	96 (98.0%)	281 (100%)	
Score 1	2 (2.0%)	0 (0.0%)	
Diffuse redness			p<0.05
Score 0	5 (5.1%)	1 (0.4%)	
Score 1	3 (3.1%)	9 (3.2%)	
Score 2	90 (91.8%)	271 (96.4%)	

*By Chi-square test

Table 3. Comparison of Undifferentiated + Severe Atrophy Group with the Undifferentiated + Non-severe Group.

	Undifferentiated + severe atrophy group (n=29)	Undifferentiated + non-severe atrophy group (n=104)	p value*
Gender (males/females)	16 (55.2%)/13 (44.8%)	54(51.9%)/50(48.1%)	n.s.
Age, years (mean±SD)	68.9±10.9	60.5±11.1	<0.01
Treatment: Surgical/Endoscopic	28 (96.6%)/1 (3.4%)	101 (97.1%)/3 (2.9%)	n.s.
Pathological findings			
Location: U/M/L	4 (13.8%)/16 (55.2%)/9 (31.0%)	6 (5.8%)/70 (67.3%)/28 (26.9%)	n.s.
Macroscopy: elevated (0-I, 0-IIa)/depressed (0-IIb, 0-IIc, 0-III) lesion	4 (13.8%)/25 (86.2%)	2 (1.9%)/102 (98.1%)	n.s.
Histopathology: por1/por2/sig/muc	2 (6.9%)/22 (75.9%)/5 (17.2%)/0	9 (8.7%)/44 (42.3%)/49 (47.1%)/2 (1.9%)	<0.05
Size (mean±SD): major axis (mm)/minor axis (mm)	41.2±25.2/28.0±17.8	30.4±22.6/19.4±15.5	<0.05/<0.05
Depth: mucosa/submucosa	16 (55.2%)/13 (44.8%)	65 (62.5%)/39 (37.5%)	n.s.
Ulceration: yes/no	12 (41.4%)/17 (58.6%)	55 (52.9%)/49 (47.1%)	n.s.
Vascular invasion: yes/no	5 (17.2%)/24 (82.8%)	4 (3.8%)/100 (96.2%)	<0.05
Endoscopic findings			<0.05
Color of the lesion: faded/reddish	12 (41.4%)/17 (58.6%)	67 (64.4%)/37 (35.6%)	
H. pylori infection: positive/negative/post eradication	21(100%)/0/0 (Unknown 8)	77(93.9%)/3(3.7%)/2(2.4%) (Unknown 22)	n.s.
Results of *Kyoto classification*			
n	23	75	
Atrophy: Score 0/1/2	0/0/23(100%)	3(4.0%)/54(72.0%)/18(24.0%)	<0.01
Intestinal metaplasia: Score 0/1/2	9(39.1%)/4(17.4%)/10(43.5%)	50(66.7%)/16(21.3%)/9(12.0%)	<0.01
Enlarged fold: Score 0/1	19(82.6%)/4(17.4%)	52(69.3%)/23(30.7%)	n.s.
Nodularity: Score 0/1	23(100%)/0	73(97.3%)/2(2.7%)	n.s.
Diffuse redness: Score 0/1/2	0/0/23(100%)	5(6.7%)/3(4.0%)/67(89.3%)	n.s.

Data are number of patients (%) unless otherwise specified.
*By Chi-square test or Mann-Whitney test

patients with severe atrophic gastritis was significantly higher in the well-differentiated cancer group. As to the endoscopic findings, the proportion of patients with high scores for atrophy, intestinal metaplasia and diffuse redness was significantly higher in the well-differentiated group. In contrast, the number of patients with higher scores for enlarged folds and nodularity was significantly higher in the undifferentiated group.

Table 3 shows the results of the comparison of the undifferentiated+severe atrophy group and undifferentiated+non-severe atrophy group. The male: female ratio was similar in the two groups (severe atrophy group: 1.2, non-severe atrophy group: 1.1). However, the patients in the severe atrophy group (68.9 ± 10.9 years) were significantly older than those in the non-severe atrophy group (60.5 ± 11.1 years). With regard to treatment, one patient in the severe atrophy group and three patients in the non-severe atrophy group underwent endoscopic submucosal dissection, while most patients

Table 4. Comparison between the Undifferentiated + Severe Atrophy Group and the Well-differentiated + Severe Atrophy Group.

	Undifferentiated + severe atrophy group (n=29)	Well-differentiated + severe atrophy group (n=223)	p value*
Gender (males/females)	16 (55.2%)/13 (44.8%)	177 (79.4%)/46 (20.6%)	<0.05
Age, years (mean±SD)	68.9±10.9	71.2±8.3	n.s.
Treatment: Surgical/Endoscopic	28 (96.6%)/1 (3.4%)	70 (31.4%)/153 (68.6%)	<0.001
Pathological findings			n.s.
Location: U/M/L	4 (13.8%)/16 (55.2%)/9 (31.0%)	24 (10.8%)/125 (56.1%)/74 (33.2%)	n.s.
Macroscopy: elevated (0-I, 0-IIa)/depressed (0-IIb, 0-IIc, 0-III) lesion	4 (13.8%)/25 (86.2%)	80 (35.9%)/143 (64.1%)	n.s.
Histopathology			
Size (mean±SD): major axis (mm)/minor axis (mm)	41.2±25.2/28.0±17.8	24.0±20.4/17.8±15.5	<0.001/<0.001
Depth: mucosa/submucosa	16 (55.2%)/13 (44.8%)	167 (74.9%)/56 (25.1%)	<0.05
Ulceration yes/no	12 (41.4%)/17 (58.6%)	45 (20.2%)/178 (79.8%)	<0.05
Vascular invasion yes/no	5 (17.2%)/24 (82.8%)	7 (3.1%)/216 (96.9%)	<0.05
Endoscopic findings			<0.001
Color of the lesion: faded/reddish	12 (41.4%)/17 (58.6%)	28 (12.6%)/195 (87.4%)	
H. pylori infection: positive/negative/post eradication	21(100%)/0/0 (Unknown 8)	113(75.4%)/35(23.3%)/2(1.3%) (Unknown 73)	n.s.
Results of *Kyoto classification*			
n	23	182	
Atrophy: Score 0/1/2	0/0/23(100%)	0/0/182(100%)	n.s
Intestinal metaplasia: Score 0/1/2	9(39.1%)/4(17.4%)/10(43.5%)	78(42.8%)/44(24.2%)/60(33.0%)	n.s
Enlarged fold: Score 0/1	19(82.6%)/4(17.4%)	168(92.3%)/14(7.7%)	n.s.
Nodularity: Score 0/1	23(100%)/0	182(100%)/0	n.s.
Diffuse redness: Score 0/1/2	0/0/23(100%)	0/2(1.1%)/180(98.9%)	n.s.

Data are number of patients (%) unless otherwise specified.
*By Chi-square test or Mann-Whitney test

in both groups underwent surgical resection. In both groups, many lesions were located in the M region and were macroscopically of the depressed type. However, the lesions were significantly larger in the severe atrophy group. The depth of invasion was limited to the mucosa in 16 patients (55.2%) and submucosa in 13 patients (44.8%) in the severe atrophy group versus 65 (62.5%) and 39 (37.5%) patients, respectively, in the non-severe atrophy group (a significantly higher percentage of submucosal tumors in the severe atrophy group). There were no significant differences in the proportion of patients with ulcer-in-cancer between the two groups. With regard to tumor histopathology, the rate of por2 tumors was significantly higher in the atrophy group [22 patients (75.9%)], while the rate of sig tumors was significantly higher in the non-severe atrophy group [49 patients (47.1%)] compared with the other group. Venous invasion was positive in five patients (17.2%) and negative in 24 patients (82.8%) in the severe atrophy group, compared with positive findings in four patients (3.8%) and negative findings in 100 patients (96.2%) in the non-severe atrophy group, with a significantly higher proportion of positive patients in the severe atrophy group. Finally, a significant difference was noted in the tumor color between the two groups: the proportion of reddish lesions was 58.6% (n=17) in the severe atrophy group, compared with 35.6% (n=37) in the non-atrophy group. There were no significant differences in the scores for enlarged folds, nodularity or diffuse redness between the two groups according to the evaluation based on the Kyoto classification.

Table 4 compares the data for the undifferentiated+severe atrophy group and well-differentiated+severe atrophy group. The male : female ratio was significantly lower in the undifferentiated group (1.2) than in the well-differentiated group (3.8), whereas the proportion of depressed lesions was not significantly different between the two groups (undifferentiated group: 86.2%, well-differentiated group: 64.1%). Many lesions in the undifferentiated group were macroscopically of the depressed type. Meanwhile, the lesions were significantly larger in the undifferentiated type group, and a significantly larger proportion of lesions in the undifferentiated group invaded the submucosa, compared with that seen in the well-differentiated group (well-differentiated group: mucosal: 74.9%, submucosal: 25.1%, undifferentiated group: 55.2%, 44.8%, respectively). The proportions of lesions with ulcer-in-cancer and venous invasion were also significantly higher in the undifferentiated group than in the well-differentiated group (ulceration: 41.4% versus 20.2%, venous-invasion: 17.4% versus 3.1%, in the undifferentiated group and well-differentiated group, respectively). However, there were no significant differences in any of the items on the Kyoto classification evaluated in this study.

We now present a typical case of undifferentiated gastric cancer and severe atrophic gastritis. A 71-year-old woman underwent screening with upper gastrointestinal endoscopy, which revealed a faded map-like area on the posterior wall (greater curvature) in the lower body of the stomach. Preoperative endoscopy showed severe atrophic gastritis (O-2) affecting the background mucosa. A 0-IIc lesion was noted, which extended from the posterior wall of the gastric angle to the greater curvature. No clear differences were noted in the color or surface (elevation/depression) of the gastric lesion compared with the surrounding mucosa, and thus a standard observation alone may have missed the lesion. Subsequently, a close examination of small intralesional ulcers demonstrated slight depression of the area around the ulcer with a faded color of the mucosa. The lesion became more distinct after indigo carmine staining, although it was still difficult to delineate the borders. Poorly differentiated cancer

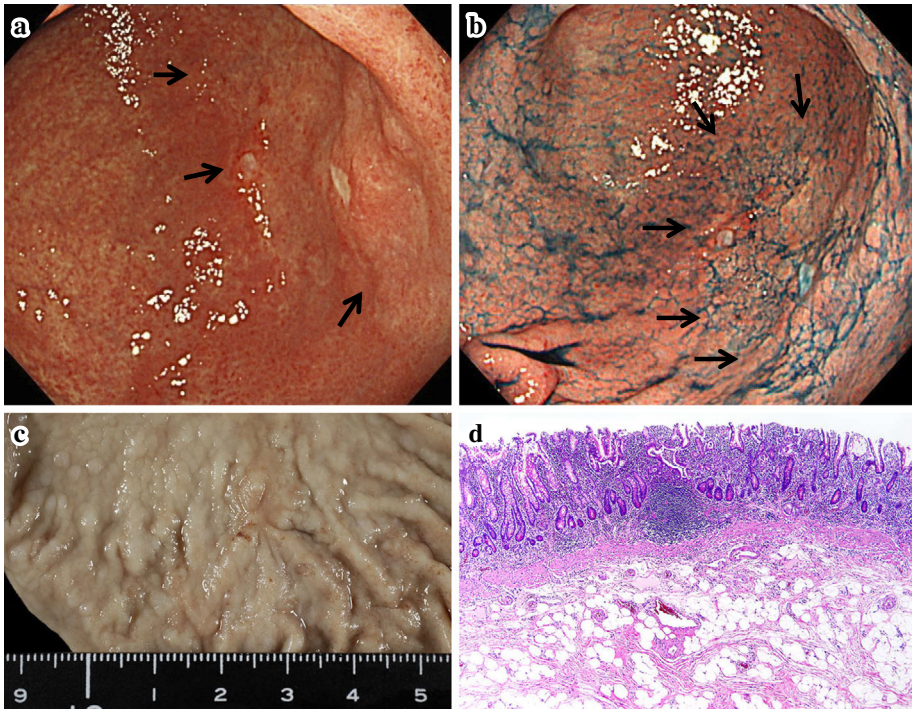

Figure. **Findings in the reported patient. (a) Endoscopic appearance of type O-IIc gastric cancer and severe background atrophic gastritis. No clear differences were noted in the color or surface of the lesion (arrows). (b) Depressed lesion was clearly seen by indigocarmine staining (arrows). (c) Resected specimen. (d) Histopathological examination showed poorly differentiated adenocarcinoma. Magnification ×10.**

was diagnosed based on a biopsy, and the patient underwent laparoscopic distal partial gastrectomy. A postoperative histopathological examination showed poorly defined and differentiated adenocarcinoma (por2) limited to the mucosa (Figure).

Discussion

In the present study, the use of endoscopy in patients with undifferentiated early gastric cancer confirmed the presence of severe atrophic gastritis in 21.8% of the subjects and moderate or severe atrophic gastritis in 78.9% of the subjects. An evaluation of the endoscopic findings obtained based on the Kyoto classification identified intestinal metaplasia in 39.8% of the patients, with enlarged folds and nodularity, which are generally considered to be associated with an increased risk of undifferentiated cancer (3, 4), in 27.6% and 2.0% of the patients, respectively. Compared with that seen in the patients in the mild-to-moderate atrophic gastritis group with undifferentiated cancer, poorly differentiated adenocarcinoma with an ambiguous glandular duct architecture, venous invasion and reddish lesions was found in significantly more patients in the severe atrophic gastritis group with undifferentiated cancer, and the tumors in these patients were significantly larger and showed deeper invasion. Even in the patients with severe atrophic gastritis, the gastric tumors were significantly larger, with deeper invasion, and significantly more lesions exhibited concomitant UL and venous invasion among the patients with undifferentiated cancer than in those with well-differentiated cancer. These findings suggest the following two points. (1) While it is widely believed that the background mucosa in patients with undifferentiated cancer is generally non-atrophic and without intestinal metaplasia (5), undifferentiated cancer arises against a background of atrophic gastritis and intestinal metaplasia more often than expected. (2) Obtaining early detection of undifferentiated gastric cancer may be relatively difficult against a background of severe atrophic gastritis, as many of the undifferentiated tumors in the patients with severe atrophic gastritis were slightly more advanced than those noted in the patients without severe gastritis. Inoue et al. (6) evaluated the background mucosa in patients with gastric cancer detected on screening and reported the presence of open-type atrophic gastritis in many patients with undifferentiated cancer as well as those with well-differentiated cancer. Therefore, it has already been reported (and the present findings support these findings) that undifferentiated cancer can develop within the background of a severely atrophic mucosa, such as that involving intestinal metaplasia or open-type atrophic gastritis, which is generally thought to be associated with well-differentiated cancer.

With regard to the color of undifferentiated cancer tissue, the lesions tended to be reddish in the severe atrophy group and faded in the non-severe atrophy group. Early undifferentiated gastric cancer often appears faded in color on endoscopy. However, Doyama et al. (7) reported that many early

undifferentiated gastric cancers arising from atrophic mucosa are reddish in color. The present findings may have been influenced by the whitish color of the background mucosa due to the effects of severe atrophy and based on the fact that the tumors in the severe atrophy group were slightly more advanced than those observed in the other patients. Identifying differences between the lesion and the background mucosa (color, unevenness, etc.) allows for the early detection of gastric cancer. Our results regarding the color of the lesion may be related to the fact that faded lesions are easier to see when the background mucosa is red (mild atrophy) and reddish lesions are easier to identify when the background mucosa is whitish (severe atrophy). In addition, small lesions tend to be faded in color and tumors become larger over time with the formation of UL as well as malignant transformation, resulting in the development of regenerating epithelium that is reddish in color.

The identification of the tumor border is reported to be less accurate, regardless of histology, when the background mucosa shows atrophic gastritis or intestinal metaplasia (8, 9). Many reports have been published in recent years on the usefulness of magnifying endoscopy combined with narrow band imaging (NBI magnifying endoscopy) for identifying the borders of early undifferentiated gastric cancer tumors, particularly undifferentiated cancer arising from the fundic gland mucosa with mild atrophy. However, some groups have reported the limited value of NBI magnifying endoscopy for identifying lesions arising against a background of atrophy or intestinal metaplasia and lesions with a small undifferentiated cancer component, as well as undifferentiated cancers without atrophy or destruction of the glandular ducts (10-12). In contrast, it was recently reported that careful endoscopic observation under white light combined with a biopsy is useful for detecting undifferentiated cancer (13). Therefore, conducting a thorough examination of the mucosa using standard endoscopy under white light, together with an appropriate biopsy, is important for avoiding the failure to detect differences in color and surface unevenness, which could assist in the diagnosis of undifferentiated cancer.

It has been reported that more than half of depressed undifferentiated cancers measuring>16 mm in size show submucosal invasion (14), suggesting that is important to detect these lesions when they are small. For the early detection of gastric cancer with endoscopy, it is important to assess the presence or absence of atrophic gastritis. However, it is necessary not to cling excessively to the common belief that well-differentiated cancer develops in patients with atrophic gastritis and undifferentiated cancer arises in cases of non-atrophic gastritis. Instead, it is important to understand that some undifferentiated cancers develop in patients with severe atrophic gastritis and that it is difficult to detect such cancers at an early stage without appropriate training.

The authors state that they have no Conflict of Interest (COI).

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