Effects of Helicobacter pylori Infection on Mucin Phenotype of Early Differentiated Gastric Carcinoma; Study with Gastric Mucosal Specimens Obtained by Endoscopic Mucosal Resection

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Key Words : early gastric cancer, Helicobacter pylori, mucin phenotypic expression, endoscopic mucosal resection (EMR)

ABSTRACT

We investigated the effect of Helicobacter pylori (H. pylori) infection on development of early differentiated gastric cancer with regard to mucin phenotypic expression and cancer's surrounding mucosa. The H. pylori antibody (HP-Ab) positive rate of patients with gastric cancer was significantly higher than that of control. Furthermore, we classified the gastric cancer group according to mucin histochemistry and immunohistochemistry into 3 types, namely gastric type, intestinal type and gastric-intestinal type whose occurrence rates were 34%, 35% and 31%, respectively. The surrounding mucosa of the intestinal phenotype cancer showed severe atrophy and high degree of intestinal metaplasia but its H. pylori density was very low. On the contrary, the surrounding mucosa of the gastric phenotype cancer revealed mild atrophy and mild intestinal metaplasia whereas the H. pylori density was relatively high. However, no statistically significant difference was observed in HP-Ab positive rate between these cancer types. Moreover, we found that the tumor diameter was inversely correlated with the incidence of the gastric phenotype cancer.

These results indicate that intestinal phenotype cancer is related to atrophy and intestinal metaplasia of surrounding mucosa caused by H. pylori infection. Furthermore, we conclude that gastric phenotype cancer is associated with the early stage of H. pylori infection but not atrophy nor intestinal metaplasia.
Introduction

The World Health Organization (WHO)/International Agency for Research on Cancer (IARC) announced that *Helicobacter pylori* (*H. pylori*) is a possible Group 1 definite carcinogen in 1994. Since then, the implication of *H. pylori* infection in gastric cancer development has been discussed. The Maastricht Consensus Report recommended eradication of *H. pylori* in patients who had undergone gastrectomy for early gastric cancer, because *H. pylori* infection is considered to be one of the major risk factors for the cancer. Furthermore, it has been demonstrated that *H. pylori* infection develops gastritis in normal gastric mucosa in animal experiments. Also, many investigators have reported that *H. pylori* infection develops atrophic gastritis according to Mongolian gerbils. However, there are a number of unknown factors involved in correlation between *H. pylori* infection and gastric cancer, especially with respect to location, macroscopic type, pathological type and mucin phenotypic expression of the lesion.

In this study, we investigated the relationship between *H. pylori* infection and development of early differentiated gastric cancer in patients who had undergone endoscopic mucosal resection (EMR), regarding macroscopic as well as pathological types of cancer, morphological variables of surrounding mucosa, mucin phenotypic expression and patient’s background. Consequently, we clarified the gastric phenotype cancer is related to the early stage of *H. pylori* infection but not atrophy nor intestinal metaplasia of surrounding mucosa of the cancer. Moreover, we found that the intestinal phenotype cancer is associated with atrophy and intestinal metaplasia of the surrounding mucosa which have been induced by *H. pylori* infection.

Subjects

Early differentiated gastric cancer patients who had undergone EMR at the Department of Internal Medicine II, Osaka Medical College between 1986 and 2003 were assigned to a gastric cancer group (137 patients). Patients who visited the department for the first time and had neither peptic ulcers nor gastric tumors observed by panendoscopy were assigned to a control group (154 patients). All patients gave informed consent.

Methods

1. **Cancer classification, patient’s background and *H. pylori* infection**

   Etiologic factors were analyzed by macroscopic type of lesion, pathological type of lesion, tumor size, patient’s age and serum *H. pylori* antibody titer between the gastric cancer group and the control group. In this study, macroscopic type of gastric cancer was classified into 2 groups, namely an elevated lesion group and a depressed lesion group. According to Japanese Classification of Gastric Carcinoma, macroscopic types I, IIa, I + IIa, and IIb were categorized into the elevated lesion group and types IIc, IIa + IIc, IIc + IIa were categorized into the depressed lesion group. Pathological type of differentiated gastric cancer was classified into 3 groups, well differentiated adenocarcinoma (tub1) group, moderate differentiated adenocarcinoma (tub2) group and papillary adenocarcinoma (pap) group. Size of gastric cancer was classified into 2 groups, a smaller lesion group (tumor diameter < 10 mm) and a larger lesion group (tumor diameter ≥ 10 mm). *H. pylori* antibody titer was measured with use of specific ELISA kit: HM-CAP (Kyowa Medex, Japan). The assay was performed according to the manufacturer’s instructions. Patients with *H. pylori* antibody titer value below 1.7 EV were classified into a negative group, and the others were into a positive group.

2. **Atrophy of gastric mucosa**

   Relationship between atrophic border and *H. pylori* infection was investigated endoscopically based on the Kimura-Takemoto classification. In this study, atrophic pattern was divided into 3 groups, mild extent group (C-1 ~ C-2), moderate extent group (C-3 ~ O-1) and severe extent group (O-2 ~ O-3). The atrophy area was designated distal site of atrophic border and non-atrophy area was also defined as proximal site of it.

3. **Mucin histochemistry and immunohistochemistry**

   Relationship between *H. pylori* infection and mucin phenotypic expression of gastric cancer was studied as follows. The specimens obtained by EMR were dissected after fixation in 10% neutral buffered formalin fixative. In terms of mucin histochemistry, high-iron diamine-alcian blue (HID; pH 2.5) stain was used for the detection of sialomucin and sulfomucin. Positivity for these mucins indicates intestinal
phenotypic expression. Paradoxical concanavalin A (Con A) stain\(^7,8\) was used for the detection of class III mucin. Class III mucin was used as a marker indicating gastric phenotypic expression. A positive galactose oxidase Schiff (GOS) reaction was used to indicate the presence of gastric foveolar-type mucin\(^9,10\).

In terms of immunohistochemistry, the sections were stained with the monoclonal anti-MUC antibody by using an avidin-biotin peroxidase complex kit (Vector Laboratories, Burlingame, CA). Anti-MUC5AC (NeoMarkers, Fremont, CA), a mouse monoclonal antibody (clone 45MI) to a peptide core corresponding to a site on the MUC5AC human core protein, was used at a dilution of 1/100. MUC5AC (45MI) and MUC6 were examined as gastric phenotype markers, and MUC2 was examined as a intestinal phenotype marker.

Cancer with gastric phenotype was categolized by the positivity of any gastric markers, such as Con A, GOS, MUC5AC or MUC6 (Figure 1). Cancer with intestinal phenotype was determined by the positivity of the intestinal marker(s) (HID and/or MUC2) and the negativity of gastric type mucins\(^11\) (Figure 2).

Cancer with intestinal phenotype was determined by the positivity of the intestinal marker(s) (HID and/or MUC2) and the negativity of gastric type mucins\(^11\) (Figure 2).

4. Cancer's surrounding mucosa

According to the Update Sydney System\(^12\), grades of \textit{H. pylori} infection (\textit{H. pylori} density), chronic inflammation, neutrophil activity, atrophy and intestinal metaplasia of surrounding mucosa were evaluated using gastric specimens (hematoxylin-eosin staining) obtained by EMR. Surrounding mucosa within 2 mm from the cancer was evaluated, and each morphology was classified into 2 groups. In each morphology, (+)

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**Fig 1.** Early Differentiated Gastric Cancer with Gastric Phenotype (original magnification × 400)
(a) Tubular adenocarcinoma consisting of cuboidal or columnar cells arranged side by side in a manner similar to foveolar epithelial cells (HE). (b) Cancer cells are stained for human gastric mucin (45MI). (c) Cancer cells are not stained for MUC2.

**Fig 2.** Early Differentiated Gastric Cancer with Intestinal Phenotype (original magnification × 400)
(a) Tubular adenocarcinoma consisting of columnar cells with eosinophilic cytoplasm resembles pyloric glands. Striated cell borders are evident (HE). (b) Cancer cells are not stained for human gastric mucin (45MI). (c) Cancer cells are stained for MUC2.
and (++) represents “Normal” plus “Mild” grades and “Moderate” plus “Marked” grades of the Update Sydney System, respectively.

5. Statistical analysis

The p values were calculated using $\chi^2$ test, and significant difference was indicated when p<0.05.

Results

1. Relationship between patient’s background, gastric cancer and H. pylori antibody titer

To clarify the effects of patient’s age and macroscopic as well as pathological cancer types on $H. \text{ pylori}$ antibody positive rate, we performed statistical analysis using $\chi^2$ test on 137 patients with gastric cancer and 154 patients suffering from neither gastric cancer nor ulcer. Age and gender had no equal distribution between the control group (154 patients, mean age: 52 years old) and the gastric cancer group (137 patients, mean age: 67 years old). The $H. \text{ pylori}$ antibody positive rate of the gastric cancer group (80%) was significantly higher than that of the control group (57%) (p<0.01), and the trend was markedly noted in younger patients (Table 1).

Next, the statistical analysis was carried out with use of macroscopic and pathological classifications to elucidate relationship between

Table 1. $H. \text{ pylori}$ Infection in Controls and Gastric Cancer Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n=154)</th>
<th>Gastric Cancer (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>HP-Ab positive rate (mean titer)</td>
<td>HP-Ab positive rate (mean titer)</td>
</tr>
<tr>
<td>~19</td>
<td>0% (0.8)</td>
<td>100% (4.0)</td>
</tr>
<tr>
<td>20~29</td>
<td>40% (2.5)</td>
<td>80% (3.7)</td>
</tr>
<tr>
<td>30~39</td>
<td>38% (2.5)</td>
<td>74% (3.8)</td>
</tr>
<tr>
<td>40~49</td>
<td>57% (3.7)</td>
<td>90% (4.3)</td>
</tr>
<tr>
<td>50~59</td>
<td>62% (3.7)</td>
<td>69% (3.4)</td>
</tr>
<tr>
<td>60~69</td>
<td>76% (3.3)</td>
<td>93% (4.4)</td>
</tr>
<tr>
<td>70~79</td>
<td>76% (3.9)</td>
<td></td>
</tr>
<tr>
<td>80~</td>
<td>70% (4.1)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>57% (3.4)</td>
<td>80% (3.9)</td>
</tr>
<tr>
<td>Patients younger than 59yo</td>
<td>* 76% (3.8)</td>
<td>69%**</td>
</tr>
<tr>
<td>Patients older than 60yo</td>
<td>81% (4.0)</td>
<td>40%</td>
</tr>
</tbody>
</table>

Mean age: Control group 52yo, Gastric cancer group 67yo. $H. \text{ pylori}$ (++) represents “Moderate” and “Marked” $H. \text{ pylori}$ density grades of the Update Sydney System. HP-Ab: $H. \text{ pylori}$ antibody. *: p<0.01, **: p<0.05

Table 2. Macroscopic Type, Pathological Type and $H. \text{ pylori}$ Infection

<table>
<thead>
<tr>
<th></th>
<th>HP-Ab positive rate (mean titer)</th>
<th>$H. \text{ pylori}$ (++) rate in surrounding mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=154)</td>
<td>57% (3.4)**</td>
<td></td>
</tr>
<tr>
<td>Gastric Cancer (n=137)</td>
<td>80% (3.9)</td>
<td>46%</td>
</tr>
<tr>
<td>Macroscopic Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated Lesion (n=83)</td>
<td>76% (3.7)</td>
<td>46%</td>
</tr>
<tr>
<td>Depressed Lesion (n=54)</td>
<td>87% (4.1)</td>
<td>46%</td>
</tr>
<tr>
<td>Pathological Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tub1 (n=117)</td>
<td>79% (3.8)</td>
<td>46%</td>
</tr>
<tr>
<td>tub2 (n=7)</td>
<td>86% (4.2)</td>
<td>71%</td>
</tr>
<tr>
<td>pap (n=13)</td>
<td>83% (4.0)</td>
<td>31%</td>
</tr>
</tbody>
</table>

Elevated Lesion contains Types I , II a, I + II a and II b. Depressed Lesion contains Types II c, II a + II c and II c+ II a of Japanese Classification of Gastric Carcinoma. $H. \text{ pylori}$ (++) represent “Moderate” and “Marked” $H. \text{ pylori}$ density grades of the Update Sydney System. HP-Ab: $H. \text{ pylori}$ antibody. *: p<0.01
the gastric cancer types and the \textit{H. pylori} antibody positive rate. In terms of macroscopic type of gastric cancer, we found no statistically significant difference in the \textit{H. pylori} antibody positive rate between the elevated lesion group (76% (63/83)) and the depressed lesion group (87% (47/54)). We also observed no statistically significant difference in the \textit{H. pylori} antibody positive rate between any pathological type of gastric cancer. The positive rates were 79% (92/117), 86% (6/7) and 85% (11/13) in the tub1 group, the tub2 group and the pap group, respectively (Table 2).

In order to demonstrate relationship between tumor diameter and \textit{H. pylori} antibody positive rate, we analyzed the same patients groups. The \textit{H. pylori} antibody positive rate was 81% (50/62) of the smaller lesion group and 80% (60/75) of the larger lesion group. However, there was no statistically significant difference between these parameters (Figure 3).

2. Area of gastric mucosal atrophy and distribution of gastric lesions

To study the relationship between area of gastric mucosal atrophy and distribution of the gastric lesions, the macroscopic diagnosis was carried out. The large number of the lesions was observed in atrophy area by the endoscopic examination. The rates of the lesions in atrophy area were 67% (4/6), 93% (25/27) and 100% (104/104) in mild extent (C-1 ~ C-2), moderate extent (C-3 ~ O-1) and severe extent (O-2 ~ O-3) of atrophy, respectively (Figure 4).

![Figure 3](image1)

**Figure 3.** Tumor diameter and \textit{H. pylori} Infection

HP-Ab: \textit{H. pylori} antibody. \textit{H. pylori} (++) represents “Moderate” and “Marked” \textit{H. pylori} density grades of the Update Sydney System. *: p<0.05

![Figure 4](image2)

**Figure 4.** Distribution of Gastric Lesion and Extent of Gastric Mucosal Atrophy

Endoscopic atrophic patterns are classified by Kimura-Takemoto’s classification as described in “Methods”.


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3. Mucin histochemistry and immunohistochemistry

To evaluate the relationship between *H. pylori* antibody positive rate and mucin phenotypic expression, the incidence of gastric, intestinal and gastric-intestinal phenotypes was compared. Based on mucin histochemistry and immunohistochemistry, the gastric cancers were classified into gastric phenotype, intestinal phenotype and gastric-intestinal phenotype. The rates of gastric, intestinal, and gastric-intestinal phenotypes were 34% (46/137), 35% (48/137) and 31% (43/137), respectively. The *H. pylori* antibody positive rates were 74% (34/46) in gastric phenotype, 85% (41/48) in intestinal phenotype and 81% (35/43) in gastric-intestinal phenotype. Thus, there was also no statistically significant difference in the antibody positive rate among these 3 groups (Table 3).

To show the correlation of tumor diameter and mucin phenotypic expression, the statistical analysis was performed. Smaller lesions were observed in 65% (30/46) of the gastric cancer with gastric phenotype, 40% (19/48) of the cancer with intestinal phenotype and 30% (13/43) of the cancer with gastric-intestinal phenotype. Statistical analysis revealed the significant differences in lesion size between gastric and the other phenotypes (p<0.05) (Figure 5).

Table 3. Mucin Phenotypic Expression and *H. pylori* Infection

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>G Type (n=137)</th>
<th>I Type</th>
<th>G-I Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP-Ab positive rate (mean titer)</td>
<td>34/46=74% (3.5)</td>
<td>41/48=85% (4.0)</td>
<td>35/43=81% (4.2)</td>
</tr>
</tbody>
</table>

Classification of gastric cancer into 3 phenotypes was carried out as described in “Methods”. G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype. HP-Ab: *H. pylori* antibody.

Fig 5. Size of Cancer and Mucin Phenotypic Expression

G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype. *, p<0.05
4. Cancer's surrounding mucosa

According to the pathological examination of the above-mentioned mucin phenotypic expression and surrounding mucosa, atrophy (+) and (++) in gastric phenotype accounted for 52% (24/46) and 48% (22/46), respectively. On the other hand, atrophy (+) and (++) were 25% (12/48) and 75% (36/48) in intestinal phenotype, and 35% (15/43) and 65% (28/43) in gastric-intestinal phenotype, respectively (Figure 6).

Intestinal metaplasia (+) and (++) accounted for 85% (39/46) and 15% (7/46) in gastric phenotype, respectively. Intestinal metaplasia (+) and (++) were 21% (10/48) and 79% (38/48) in intestinal phenotype, and (+) and (++) were 51% (22/43) and 49% (21/43) in gastric-intestinal phenotype, respectively. Compared with the cancer with gastric phenotype, intestinal metaplasia was significantly higher in the cancer with intestinal and gastric-intestinal phenotypes (each p<0.01) (Figure 7).

Fig 6. Atrophy of Surrounding Mucosa and Mucin Phenotypic Expression
Atrophy (+) represents “Normal” and “Mild” atrophy grades, and Atrophy (++) represents “Moderate” and “Marked” atrophy grades of the Update Sydney System. G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype.

Fig 7. Intestinal Metaplasia in Surrounding Mucosa and Mucin Phenotypic Expression
Int. Metaplasia (+) represents “Normal” and “Mild” intestinal metaplasia grades, and Int. Metaplasia (++) represents “Moderate” and “Marked” intestinal metaplasia grades of the Update Sydney System. G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype. *: p<0.01
In terms of *H. pylori* infection in surrounding mucosa, (+) and (++) were 35% (16/46) and 65% (30/46) in gastric phenotype, respectively. The *H. pylori* (+) and (++) were 65% (31/48) and 35% (17/48) in intestinal phenotype, in addition to 63% (27/43) and 37% (16/43) in gastric-intestinal phenotype, respectively. Compared with intestinal phenotype and gastric-intestinal phenotype, *H. pylori* density was significantly higher in the cancer with gastric phenotype (each p<0.05) (Figure 8).

Mononuclear cells (+) and neutrophils (+) were noted in all phenotypes. This means that chronic inflammation and neutrophil activity were mild in all phenotypes (Figure 9, 10).

5. *H. pylori* density in surrounding mucosa

To elucidate the effect of age on *H. pylori* infection, *H. pylori* density in surrounding mucosa of the gastric cancer patients was compared between younger (<60 years old) and older (≥60 years old) groups. The rates of *H. pylori* (++) were 69% (20/29) and 40% (43/108) in younger and older groups, respectively. Thus, the *H. pylori* density was significantly higher in younger group (p<0.05). However, there was no statistically significant difference in *H. pylori* antibody positive rate between younger group 76% (22/29) and older group 81% (88/108) (Table 1).

We analyzed the correlation of macroscopic as well as pathological types of the cancer and *H. pylori* density. In terms of macroscopic type of gastric cancer, the patients were divided into 2 groups, namely the elevated lesion group and the depressed lesion group. The rates of *H. pylori* (++) in the elevated group and the depressed lesion group were 46% (38/83) and 66% (25/38), respectively. In terms of pathological type of gastric cancer, the patients were classified into 3 groups, i.e. the tub1 group, the tub2 group and the pap group. The rates of *H. pylori* (++) in the tub1, tub2 and pap groups were 46% (54/117), 71% (57/75) and 31% (41/13), respectively. No relationship was noted between the macroscopic type, pathological type and the *H. pylori* density (Table 2).

Moreover, the relationship between tumor diameter and *H. pylori* density was studied. The rates of *H. pylori* (++) in the surrounding mucosa was 56% (35/62) in smaller lesions and 37% (28/75) in larger lesions. A statistically significant difference was noted between them (p<0.05) (Figure 3).

Discussion

It is well known that *H. pylori* infection is one of the risk factors for gastric cancer, but actual relationship between gastric cancer and *H. pylori* infection is unclear, especially with respect to location of lesion, endoscopic type, histopathological type, and mucin phenotypic expression. We investigated here the relationship between *H. pylori* density in Surrounding Mucosa and Mucin Phenotypic Expression

**Fig 8.** *H. pylori* density in Surrounding Mucosa and Mucin Phenotypic Expression

*H. pylori* (+) represents “Normal” and “Mild” *H. pylori* density grades, and *H. pylori* (++) represents “Moderate” and “Marked” *H. pylori* density grades of the Update Sydney System. G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype. *: p<0.05
pylori infection and development of early differentiated gastric cancer concerning cancer size, mucin histochemistry, immunohistochemistry and morphological variables of surrounding mucosa.

The H. pylori antibody positive rates were 57% in the control group and 80% in the gastric cancer group (Table 1). It was significantly higher in the gastric cancer group, especially, more prominent in the younger group. This result supports a high odds ratio that indicates relationship between gastric cancer and H. pylori infection. Forman and Parsonnet have also reported the similar results in their prospective study.

Next, we classified the early gastric cancer according to mucin phenotypic expression and studied relationship with H. pylori infection. By the mucin histochemical and immunohistochemical methods, several groups have revealed that the incidence of the gastric cancer with gastric phenotype is significantly higher than that of the previous reports. Our results indicate that the early differentiated gastric cancer with gastric phenotype was observed in 34% of the gastric cancer patients. The cancers with intestinal

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**Fig 9. Mononuclear Cells in Surrounding Mucosa and Mucin Phenotypic Expression**
Mononuclear Cells (+) represents “Normal” and “Mild” inflammation grades, and Mononuclear Cells (++) represents “Moderate” and “Marked” inflammation grades of the Update Sydney System. G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype.

**Fig 10. Neutrophils in Surrounding Mucosa and Mucin Phenotypic Expression**
Neutrophils (+) represents “Normal” and “Mild” activity grades, and Neutrophils (++) represents “Moderate” and “Marked” activity grades of the Update Sydney System. G Type: gastric phenotype. I Type: intestinal phenotype. G-I Type: gastric-intestinal phenotype.
phenotype and gastric-intestinal phenotype were observed in 35% and 31% of the patients, respectively (Table 3). These results indicate that the gastric cancer with gastric phenotype including gastric-intestinal phenotype was observed in 65% of the gastric cancer patients.

With regard to mucin histochemistry and immunohistochemistry, it was reported that continuous \textit{H. pylori} infection caused atrophy of gastric mucosa and/or intestinal metaplasia and it lead finally to differentiated gastric cancer with intestinal phenotype with high probability\textsuperscript{17-21}. However, Table 3 shows that \textit{H. pylori} antibody titer, which is one of the indicators of \textit{H. pylori} infection rate, was not high in the differentiated gastric cancer with intestinal phenotype. Moreover, statistical analysis revealed no significant difference between the intestinal phenotype and gastric phenotype. We indicate that \textit{H. pylori} infection may be related to gastric cancer with both gastric phenotype and intestinal phenotype.

Cancer’s surrounding mucosa was evaluated according to the Update Sydney System. Severe atrophy was observed in 48% of the gastric cancer with gastric phenotype, 75% of that with intestinal phenotype, and 65% of that with gastric-intestinal phenotype (Figure 6). Atrophy of the surrounding mucosa was tended to be stronger in the gastric cancer with intestinal phenotype. Severe intestinal metaplasia was noted in 15% of the cancer with gastric phenotype, 79% of the cancer with intestinal phenotype, and 49% of the cancer with gastric-intestinal phenotype (Figure 7). Compared with the cancer with gastric phenotype, intestinal metaplasia was significantly greater in the gastric cancer with intestinal type. In other words, atrophy and intestinal metaplasia in the surrounding mucosa of the cancer with gastric phenotype were mild but its \textit{H. pylori} density was significantly high. On the other hand, atrophy and intestinal metaplasia were severe in surrounding mucosa of the gastric cancer with intestinal phenotype, but its \textit{H. pylori} density was low. These results support that the differentiated gastric cancer with intestinal phenotype develops atrophy of gastric mucosa and/or intestinal metaplasia associated with continuous \textit{H. pylori} infection.

It has been reported that undifferentiated cancer with gastric phenotype, which mostly develops in gastric glands, has neither atrophic gastritis nor intestinal metaplasia\textsuperscript{20}. In this study, the differentiated cancer with gastric phenotype also showed the same result. Our observation is in good agreement with the reports by Egashira\textsuperscript{17}, Nishikura et al.\textsuperscript{22}, and Tsuji et al.\textsuperscript{23} that differentiated cancer with gastric phenotype changes into undifferentiated cancer according to cancer development.

The \textit{H. pylori} density of the cancer with gastric phenotype was significantly higher than that of the cancer with not only intestinal phenotype but also gastric-intestinal phenotype (Figure 8). These results indicate that \textit{H. pylori} infection may have some effects on development of the cancer with gastric phenotype. It also supported the theory by Nishikura et al.\textsuperscript{22,24} that \textit{H. pylori} was observed in proper gastric mucosal element throughout cancer development, so \textit{H. pylori} infection could continue in cancer with gastric phenotype which produced gastric mucin.

Furthermore, the tumor diameter of the gastric cancer with gastric phenotype was small and \textit{H. pylori} density in the surrounding mucosa was high. However, the diameter of the cancer with intestinal phenotype and gastric-intestinal phenotype was large and the \textit{H. pylori} density was low. These results support the theory by Sugihara\textsuperscript{26}, Egashira\textsuperscript{27}, and Tatematsu et al.\textsuperscript{28} that minute gastric tumors, which generally show gastric phenotype at early stage, develop into gastric-intestinal phenotype as they grow by acquiring the nature of intestinal phenotype.

In conclusion, this study suggests that the \textit{H. pylori} antibody positive rate of the gastric cancer, regardless of gastric phenotype or intestinal phenotype, is higher than that of the control group. Furthermore \textit{H. pylori} infection may be related to development of the cancer with gastric phenotype as well as the cancer with intestinal phenotype. In the gastric cancer with intestinal phenotype, \textit{H. pylori} infection induced atrophy of the surrounding mucosa and the intestinal metaplasia. The continuous \textit{H. pylori} infection had some effects on carcinogenesis and growth. On the other hand, \textit{H. pylori} density in the surrounding mucosa of the gastric cancer with gastric phenotype tended to be higher than the cancer with gastric-intestinal phenotype or intestinal phenotype, and the cancer with small tumor diameter was mostly gastric phenotype. It is suggested that the early stage of \textit{H. pylori} infection may have important roles in the carcinogenesis.


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