

Prevalence of *Helicobacter pylori* infection rate in heterotopic gastric mucosa in histological analysis of duodenal specimens from patients with duodenal ulcer

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Summary. Heterotopic gastric mucosa in the duodenal bulb is a rare congenital disorder with varied clinical presentations. The mechanism of formation of a duodenal ulcer is failure of balance of the attack factor and the defense factor, which is the same as the mechanism of formation of a gastric ulcer. However, the true etiology of the duodenal ulcer remains unknown. Gastric mucosa can secrete gastric juice which injures itself, but the duodenal mucosa does not contain cells secreting a digestive enzyme. We assume that duodenal ulcers are caused by the presence of heterotopic gastric mucosa that can secrete gastric acid. This study was designed to assess the prevalence and associations of heterotopic gastric mucosa in duodenal ulcers.

The present study included 137 patients who underwent biopsy or resection of duodenal ulcer. We detected gastric foveolar metaplasia due to inflammation from a heterotopic gastric mucosa using immunohistochemical staining. Heterotopic gastric mucosa consists of foveolar epithelium (MUC5AC-positive) and fundic gland (H⁺K⁺ ATPase-positive parietal cells, pepsinogen I-positive chief cells and MUC6-positive mucous neck cells), whereas gastric metaplasia is composed of foveolar epithelium without fundic glands. These specimens were stained with toluidine blue for detection

of *Helicobacter pylori* infection.

Among the 137 patients with duodenal ulcer, 76 cases (55%) had heterotopic gastric mucosa in the obtained specimens, and *Helicobacter pylori* was found in 45 cases (59%, 45/76) among those with heterotopic gastric mucosa. Our results suggest that heterotopic gastric mucosa was strongly associated with concurrent duodenal ulcer.

Key words: Heterotopic gastric mucosa, Gastric metaplasia, Duodenal ulcer, *Helicobacter pylori*

Introduction

Heterotopic gastric mucosa (HGM) in the duodenum was first described by Schmidt in 1805 (Jadaan and Oda, 2014). It is classified as either congenital in origin due to abnormal embryological development or acquired epithelium resembling gastric mucosa of the pyloric type. Wolff (1971) reported a large series of 87 cases of gastric heterotopia in the alimentary canal, of which 15 involved the duodenum. Lessells and Martin (1982) subdivided heterotopia into congenital and acquired subtypes and reported that in the duodenum the presence of a fundic gland consisting of parietal cells and chief cells was true congenital heterotopia, but the pyloric-type epithelium with small numbers of scattered isolated parietal cells was an acquired phenomenon. It is recognized that the surface epithelium of the duodenum may change to a gastric type in duodenitis and duodenal

ulceration; this represents gastric metaplasia (GM) rather than heterotopia. Recent studies have demonstrated that metaplastic or hyperplastic epithelium of gastric mucosa is associated with frequent genetic alterations, and *GNAS* and/or *Kras* mutations were found in 28% of HGM lesions (Matsubara et al., 2015). We suppose that many studies have combined cases of metaplasia and true heterotopia because there are no strict criteria for heterotopic gastric mucosa. Hence, we need to establish diagnostic criteria of heterotopic gastric mucosa by immunohistochemical staining such as staining for mucin core protein and for a specific antigen of the fundic gland.

HGM has been reported to be observed along the length of the gastrointestinal tract (Genta et al., 2010; Terada, 2011; Colombo et al., 2018; Nasir et al., 2018). A recent endoscopic study reported that the incidence of HGM lesion was 1.9 % in the population undergoing endoscopy, whereas other studies reported that microscopic HGM was present in 0.67% up to 33% among a series of gastrectomy cases (Wolff, 1971; Spiller et al., 1982; Genta et al., 2010; Terada 2011; Conlon et al., 2013; Nasir et al., 2018). Due to recent advances in endoscopy, it is possible to diagnose HGM endoscopically, and HGM has been more frequently recognized (Terada, 2011). It has been described that HGM has various appearances, including polyps, nodules and non-specific mucosal irregularities such as an elevated or flat erythematous area with erosion and/or bleeding (Genta et al., 2010; Terada 2011; Conlon et al., 2013; Nasir et al., 2018).

Studies on HGM in duodenum were mostly carried out several decades ago, and they were individual case reports or relatively small investigations (Johansen, 1967; Ikeda et al., 1982; Genta et al., 2010). There are no recent data regarding the importance of HGM in ulcer formation. Pathologic and functional characteristics between HGM, GM, and duodenal ulcer (DU) in the duodenum remain speculative. In most instances, the DU is located on either the anterior or the posterior wall of the duodenal bulb, and the majority of HGM cases occur in the first part of the duodenum (Wolff, 1971; Saha, 2007; Genta et al., 2010; Terada 2011; Conlon et al., 2013). Interestingly, it has been reported that HGM in jejunum caused peptic ulcer which might be related to heterotopic hydrochloric acid secretion by the HGM; subsequently, hydrochloric acid induced chronic inflammation and ulceration (Yamada et al., 2009; Jadaan and Oda, 2014). Previous reports described that HGM was often functional tissue secreting gastric acid and HGM samples were frequently taken as part of biopsy or resected specimens from the edge of DU (Willis, 1968; Hoedemaeker, 1970; Wolff, 1971; Terruzzi et al., 1987; Carrick et al., 1989). In contrast, more recent investigations revealed that HGM was not associated with DU (Shousha et al., 1983; Smithuis and Vos, 1989; Wyatt et al., 1990; Conlon et al., 2013). DU is a multifactorial condition, and is associated with gender, genetic predisposition, alcohol consumption,

cigarette smoking, intake of nonsteroidal anti-inflammatory drugs, and *Helicobacter pylori* (*H. pylori*) infection (Wyatt et al., 1990). Recent studies showed that *H. pylori* infection in duodenum was a strong risk factor for the development of duodenal ulceration, and GM in the duodenum is colonized by *H. pylori*, resulting in chronic and active inflammation (Goodwin, 1988; Carrick et al., 1989; Wyatt et al., 1990; Tytgat et al., 1990; Voutilainen et al., 2003). *H. pylori* colonizes only gastric-type epithelium, and is therefore able to infect the duodenal epithelium only if either GM or HGM is present (Thomas et al., 1984; Graham, 1989; Wyatt et al., 1990).

Owing to widespread use of proton pump inhibitors (PPIs) and decreasing prevalence of *H. pylori* infection, the prevalence of DU has decreased over the past decade (Malaty, 2007). The aim of this study was to assess the prevalence and clinicopathological associations of HGM by histological examination of duodenal specimens from DU patients. We propose that *H. pylori* infects the stomach and HGM in the duodenum.

Materials and methods

Patients and tissue specimens

All of the procedures in the present retrospective study, including the use of specimens from human subjects, were approved by the Ethics Committee of the University of Occupational and Environmental Health (UOEH), Japan (permission number H29-157). Pathological reports were reviewed to identify patients who underwent surgical resection of the duodenum or biopsy of the duodenum between 1995 and 2016 at the hospital of UOEH.

This study included 137 patients who were diagnosed endoscopically with duodenal ulcer, and in whom biopsy specimens of the duodenal ulcer or surgically resected specimens of the duodenal ulcer due to bleeding or perforation were submitted for pathological analysis. The number of sections of resected duodenal ulcer tissue was examined at three average portions from the edge of ulcer. An endoscopic diagnosis of duodenal ulcer was made if one or more of the following were present: surrounding mucosa is reddened and edematously swollen; bleeding; or absence of regeneration epithelium (Voutilainen et al., 2003). Endoscopic reports were available in all cases, but an endoscopic imaging report and gross photograph were not available. Most of the biopsy and resected specimens of the duodenum were taken from the first part of the duodenum. We divided the patients into those who were 40 years old or younger and those who were over 40 years old, since the mean age at which DU develops is around 40 years old (Carrick et al., 1989). It was not feasible to collect details of follow-up history, ulcer history, smoking habit, alcohol consumption, and drug intake, since these past data did not remain.

All of the specimens were routinely fixed in 10%

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formalin, and paraffin-embedded tissue blocks were prepared by our Department of Pathology. Two pathologists examined all biopsy and resected specimens to confirm the histopathological features. These tissues were stained with hematoxylin and eosin (H&E) and toluidine blue for detection of *H. pylori* infection. Immunohistochemistry of sequential sections was also performed.

Immunohistochemistry of tissue samples

Immunohistochemical staining was performed according to the antibody-linked dextran polymer method for antibody-bridge labeling, with hematoxylin counterstaining (Histofine Simplestain Max-PO; Nichirei, Tokyo, Japan). Deparaffinized and rehydrated 4- μ m sections were incubated in 10% H₂O₂ for 5 min to block endogenous peroxidase activity. Primary antibodies used in the present study were antibodies against MUC1 (Ma552; 1:100 dilution; Novocastra, Newcastle upon Tyne, UK), MUC2 (Ccp58; 1:100 dilution; Novocastra), MUC5AC (CLH2; 1:100 dilution; Novocastra), MUC6 (CLH5; 1:100 dilution; Novocastra), H⁺K⁺ ATPase (1H9; 1:100 dilution; Medical and Biological Laboratories Co., Nagoya, Japan), pepsinogen I (8003; 1:100 dilution; Bio-Rad, Hercules, California, USA), and gastrin (1:300 dilution; DAKO, Santa Clara, California, USA), and *Helicobacter pylori* antibody (SPM526; 1:50 dilution; Novus Biologicals, Centennial, Colorado, USA). After incubation with the primary antibody at room temperature for 1 hour, sections were washed and incubated with peroxidase-labeled anti-rabbit or anti-mouse antibody (Histofine Simplestain Max-PO; Nichirei, Tokyo, Japan) at room temperature for 30 minutes. Peroxidase activity was detected with diaminobenzidine (DAB; Sigma-Aldrich, St. Louis, MO, USA). Sections were counterstained with hematoxylin and dehydrated. The sections were observed under a light microscope.

Histological studies

There are two types of gastric mucosal elements that are occasionally seen in the duodenum: GM and HGM. Duodenal bulb GM was defined as the presence of foci of MUC5AC-positive gastric-type surface epithelium containing MUC6-positive pyloric glands without fundic glands and the absence of parietal cells and chief cells. HGM was diagnosed as the presence of MUC5AC-positive gastric foveolar epithelium and at least one fully formed fundic gland consisting of H⁺K⁺ ATPase-positive parietal cells, pepsinogen I-positive chief cells and/or MUC6-positive mucous neck cells.

Duodenal inflammation was defined as the presence of polymorphonuclear neutrophils in the duodenal mucosa. Duodenal inflammation was graded according to the previously described criteria as follows: 0=none, 1=mild, 2=moderate, 3=severe (Whitehead et al., 1975;

Voutilainen et al., 2003).

There are only a few gastrin cells in the duodenum, although they are regularly seen in the proximal duodenum, and the Brunner glands contain gastrin cells and endocrine cells in low to moderate numbers (Sjölund et al., 1983). The gastrin cells were counted per visual field at an image magnification of $\times 125$, and 5-10 sections from each tissue specimen were analyzed by counting the number of gastrin cells in 10-20 visual fields in each specimen using a previously reported method (Sjölund et al., 1983).

Statistical analysis

All values are expressed as the means \pm standard error (SE). The significance of differences was analyzed using Fisher's exact test, Student's t-test, and multivariate logistic regression. $P < 0.05$ was considered as statistically significant. Hazard ratios and 95% confidence intervals (95% CIs) were estimated using univariate or multivariate Cox proportional hazard models. All statistical tests were two-tailed, with a P value of < 0.05 considered to be statistically significant. All statistical analyses were performed with the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, this program is a modified version of R commander (version 1.6-3) that had been designed to add statistical functions frequently used in biostatistics (Kanda, 2013).

All histological and immunohistochemical slides were evaluated by two independent observers using a blind protocol design (the observers were blinded to the clinicopathological data). The degree of agreement between the observers was excellent (an agreement rate of more than 95%) for all antibodies investigated, as measured according to the interclass correlation coefficient. For the very few (less than 1%) instances of disagreement, a consensus score was calculated by a third board-certified pathologist in our department.

Results

Study population and prevalence of the 137 patients with duodenal ulcers

Of the 137 patients with duodenal ulcer included in the present analysis, a total of 44 surgically resected specimens and 93 duodenal biopsy specimens were studied. The characteristics of the patients and the duodenal ulcer specimens including age, gender, location in duodenum, perforation, inflammation and presence of HGM, are summarized in Table 1. Eighty-nine patients were men and 48 were women (man:woman 1.9:1). Their mean age was 56 years (95% CI 53-59 years). The mean age of the male patients was 52 years (95% CI 48-56 years), and that of the female patients was 63 years (95% CI 59-67 years). One hundred twenty specimens (88%)

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originated from the first part of the duodenum, and 17 specimens (12%) from the second part of the duodenum. Duodenal specimens from 76 patients (55%) were positive for HGM.

Histopathological and immunohistochemical findings

To assess whether a fundic gland(s) was present, we performed immunohistochemistry to test for the presence of parietal cells, chief cells, and mucous neck cells. There was no expression of MUC1 in goblet and columnar cells of the normal duodenal epithelium, with the adjacent gastric foveolar epithelium demonstrating negative staining in all cases. Immunohistochemical staining for MUC2 was positive in the normal duodenal epithelium (i.e., in intestinal goblet cells), but foveolar epithelium was absent. MUC5AC was highly expressed in foveolar epithelium in both HGM and GM (Fig. 1B,F). Expression of MUC6 was detected in mucous neck cells in fundic glands in HGM (Fig. 1C,G). Immunohistochemistry for H⁺K⁺ ATPase and pepsinogen I, which are essential for gastric acid production, was positive in parietal cells and chief cells in fundic glands in HGM (Fig. 1D,H). No immunoreactivity for H⁺K⁺ ATPase and pepsinogen I was observed in GM (Fig. 1E,I). Gastrin was expressed in gastrin cells and enterochromaffin cells in Brunner gland and in fundic glands of HGM (Fig. 1). Staining for

gastrin was uniform and involved both the membrane and cytoplasm of the cells.

There was no significant difference in the number of

Table 1. Characteristics of the 137 patients with duodenal ulcer.

		N=137	%
Age	Range (y)	18-90	
	Median (y)	58	
	40 y<	25	18
	≤40 y	112	82
Sex	Female	48	35
	Male	89	65
Location*	first part	120	88
	second part	17	12
Perforation	+	93	68
	-	44	32
Inflammation	mild	64	47
	moderate	22	16
	severe	51	37
HGM	-	61	45
	+	76	55

*The location of the duodenal ulcer in the duodenum is shown (the duodenal ulcer was located in the first part or the second part of the duodenum). HGM, heterotopic gastric mucosa

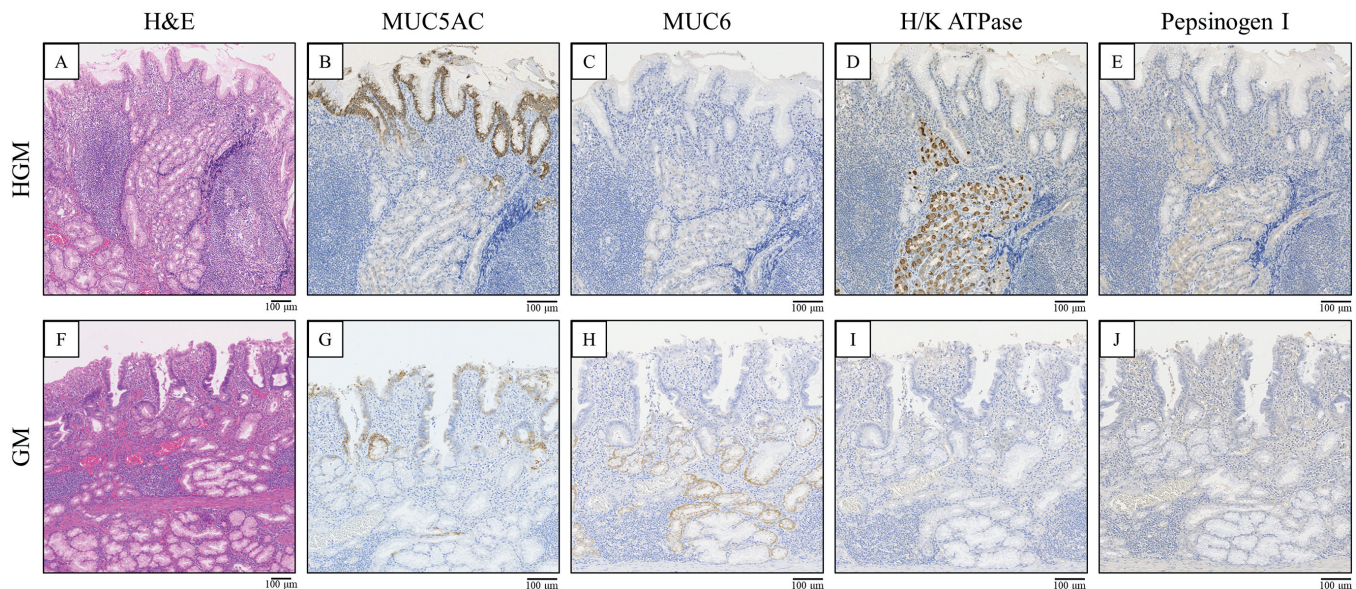


Fig. 1. A. Heterotopic gastric mucosa. F-J. Gastric metaplasia (GM). A. Heterotopic gastric mucosa (HGM) in duodenum, and interface of gastric foveolar mucosa with a fully formed fundic gland in the duodenum (Hematoxylin and eosin (H&E) stain). B. Immunohistochemical staining for MUC5AC was positive in foveolar epithelium of HGM (Immunostain). C. Expression of MUC6 was detected in mucous neck cells in the fundic gland in HGM (Immunostain). D, E. H⁺K⁺ ATPase staining was positive in parietal cells and pepsinogen I staining was positive in chief cells in the fundic gland in HGM (Immunostain). F. Gastric metaplasia (GM) in duodenum, and interface of gastric foveolar mucosa (H&E). G. Immunohistochemical staining for MUC5AC was positive in foveolar epithelium of GM (Immunostain). H. MUC6 was expressed in Brunner glands in the duodenum (Immunostain). I, J. Immunohistochemical staining for H⁺K⁺ ATPase and pepsinogen I was negative in GM (Immunostain). × 100.

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gastrin cells in the duodenum between HGM (10.6 ± 7.6 per 3.8 mm^2) and non-HGM tissues (9.6 ± 6.3 per 3.8 mm^2) ($p=0.22$) (Fig. 2).

H. pylori colonies were only seen in gastric-type epithelium in the duodenum, but not in colonic epithelium (Fig. 3).

Association between HGM and *H. pylori* infection

HGM was detected in 36 (81%) of the 44 surgically

resected specimens and in 40 (43%) of the 93 biopsy specimens. The higher prevalence of *H. pylori* infection in surgically resected specimens may have been due to the fact that more specimens could be prepared from resected specimens than from biopsy specimens. The prevalence of HGM according to age, sex, location, perforation, inflammation, and *H. pylori* infection are shown in Table 2. There were significant differences in the prevalence rates of HGM associated with location, perforation, severe inflammation and *H. pylori* infection

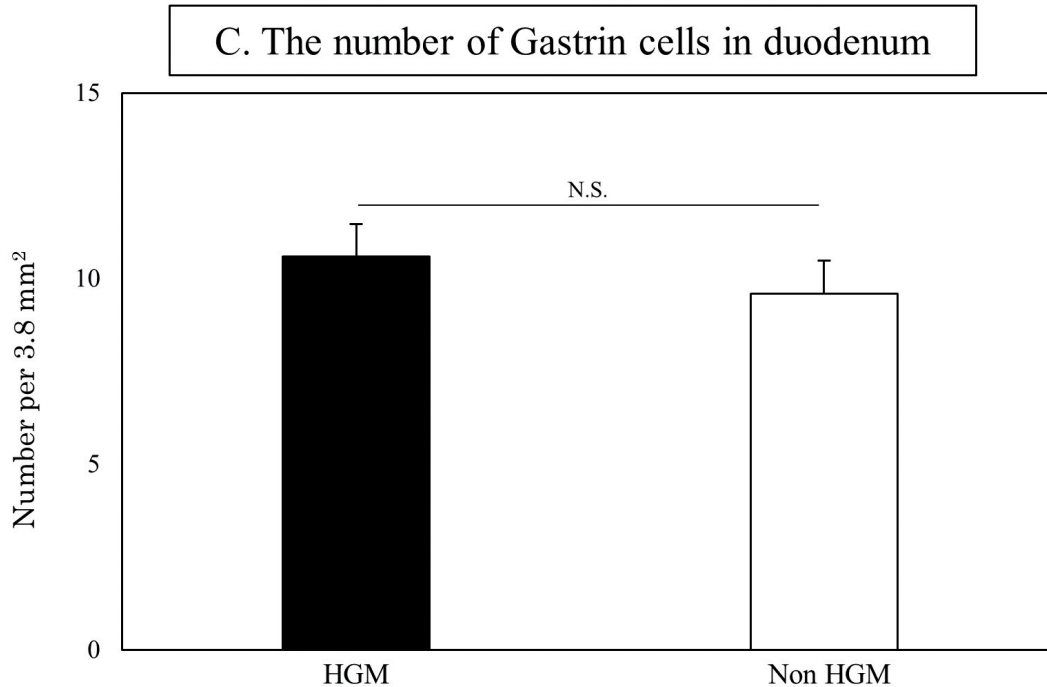
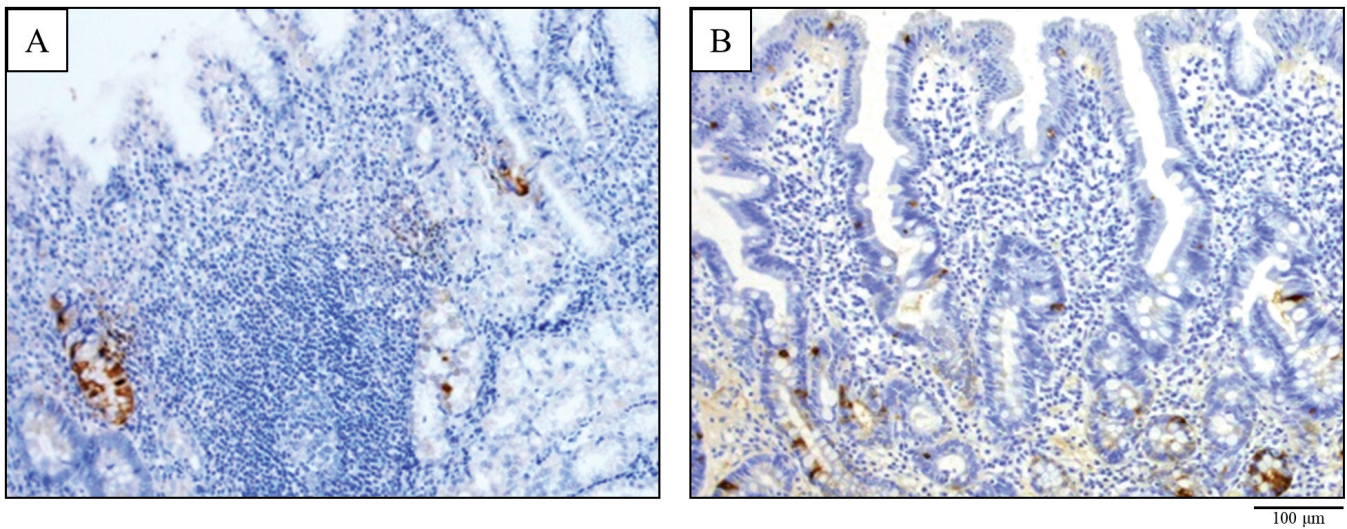


Fig. 2. Immunohistochemical staining for gastrin. A few gastrin cells were seen in both (A) HGM (Immunostain) and (B) non-HGM areas (Immunostain) in the proximal duodenum. C. The number of gastrin cells in the HGM and non-HGM areas of the duodenum did not show a significant difference. Each bar represents the mean \pm SE. N.S., not significant. $\times 100$.

using Fisher’s exact test.

Discussion

HGM was an incidental endoscopic and histopathologic finding in duodenal specimens submitted for evaluation of unrelated conditions. Recent large endoscopic studies on HGM reported an incidence of 0.67-11 % in the population undergoing endoscopy (Terada, 2011; Conlon et al., 2013; Nasir et al., 2018). In recent studies, *H. pylori* has been regarded as one of the etiological factors in the pathogenesis of DU (Saha, 2007). The clinical significance of HGM, especially in relation to DU, has not been clarified. In the present study, we defined the criteria of HGM as the immunohistochemical presence of parietal cells, chief cells and mucous neck cells. We found that HGM was more widespread than previously suspected. We also revealed that HGM was frequently found at the proximal edge of the duodenal ulcer region. *H. pylori* could colonize in HGM in the duodenum, and then the *H. pylori* infection may induce active inflammation in the duodenum. Histological examination of the duodenal specimens confirmed that ulcer formation was associated with *H. pylori* infection and HGM. The presence of HGM in the duodenum was significantly associated with *H. pylori* infection, perforation, location of DU in the first part of the duodenum, and severe inflammation, but not with age, gender, and gastrin secretion. *H. pylori* infection upregulates gastrin secretion, probably leading to increased duodenal acid load (Olbe et al., 1996). The present data suggested that *H. pylori* colonizes HGM, leading to increased inflammation in the duodenum; then parietal cells in the HGM secrete gastric acid which injures the duodenal mucosa and induces inflammation.

The earliest papers on HGM reported that HGM

was associated with DU and *H. pylori* infection (Hoedemaeker, 1970; Johansen and Hansen, 1973). However, recent studies have contradicted these associations, and suggested instead an inverse correlation between HGM and DU (Smithuis and Vos, 1989; Genta et al., 2010). Previously, DU was usually treated by resection, and the resected specimens were examined in detail to detect fundic glands. However, today, DU is predominantly treated conservatively. Therefore, we analyzed only biopsy specimens of DU that had been obtained after patients were treated with medication. In our study, the percentage of specimens with HGM among the surgically resected specimens was higher than the percentage with HGM among the biopsy specimens. We suppose that previously reported

Table 2. The prevalence of heterotopic gastric mucosa according to age, sex, location, perforation, inflammation grade, and *Helicobacter pylori* infection (as detected by histology).

		HGM		P-value
		-	+	
Age	40 y<	11	14	0.953
	≤40 y	50	62	
Sex	Female	24	24	0.372
	Male	37	52	
Location	first part	49	71	0.0347
	second part	12	5	
Perforation	-	53	40	<0.001
	+	8	36	
Inflammation	mild to moderate	46	40	0.0076
	severe	15	36	
<i>Helicobacter pylori</i>	-	41	31	0.0033
	+	20	45	

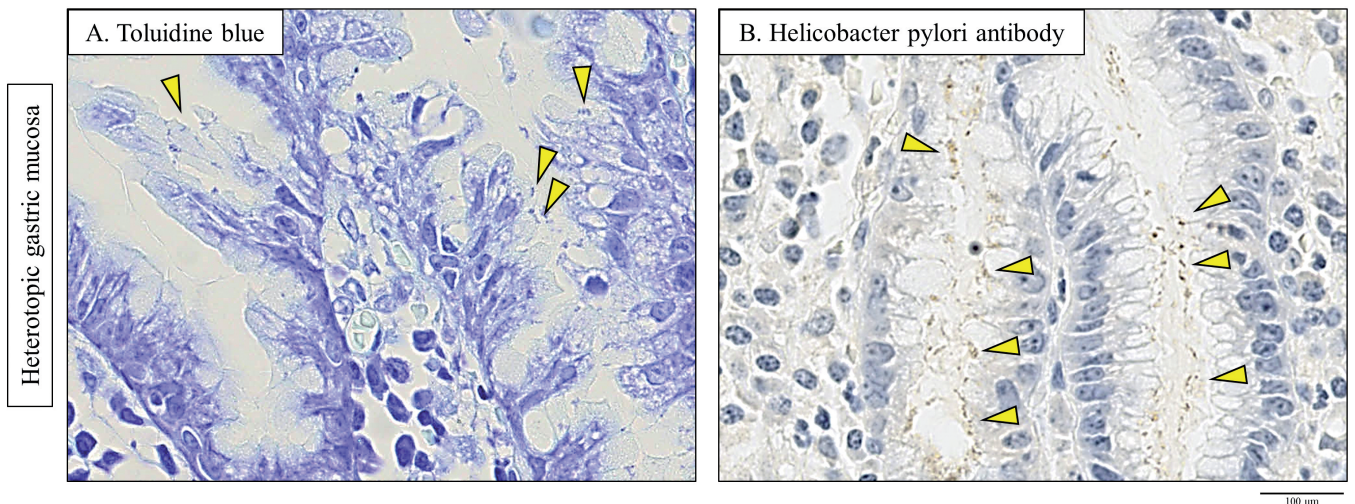


Fig. 3. A. Toluidine blue stain detected *H. pylori* colonies (yellow triangles) in gastric-type epithelium of HGM in the duodenum. B. Immunohistochemical staining for *H. pylori* (yellow triangles) was positive in gastric foveolar epithelium of HGM. × 400.

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data were not sufficiently clear to enable us to assess whether HGM was present around the duodenal ulcer or not, since the endoscopic diagnosis and endoscopic retrieval of sufficient material of HGM were difficult due to patchy distribution of HGM in the duodenum, and many of the biopsy fragments were too small and difficult to orientate (Wolff, 1971; Wyatt et al., 1990; Terada, 2011).

This study has a major limitation in its interpretation. First, this study was retrospective in nature and there was high selection bias. In Western countries and currently in Japan, treatment for duodenal ulcer is not performed by biopsy or resection of duodenal ulcer, and this study is not representative of the entire population of duodenal ulcer patients. Second, we detected the presence of HGM at the proximal edge of the duodenal ulcer region only by histology; however, the present study did not prove that the parietal cells produced gastric acid and secreted it in the duodenum. Third, we did not examine the risk factors for DU using multivariate analysis, such as *H. pylori* infection in the stomach, smoking, alcohol consumption, and drug intake. In previous reports, endoscopic analysis showed that parietal cells in the HGM secreted gastric acid, HGM was often functional tissue and its functioning parietal cells could secrete gastric acid in the duodenum (Willis, 1968; Carrick et al., 1989). Additionally, *H. pylori* infection in the stomach was shown to be associated with DU, although there were no relationships between DU and smoking, alcohol abuse, or drug intake (Blaser, 1987; Wyatt et al., 1990). Further follow-up of larger cohorts is needed to confirm the intriguing relationship between DU and HGM.

In this study, we did not study whether each case of HGM was congenital or a regenerative process. Recently, it has been suggested that a specialized fundic gland could develop in the duodenum as part of the spectrum of metaplastic change; for example, inflammation by reflux esophagitis sometimes may induce the formation of a fully formed fundic gland in the esophagogastric junction (Lupu et al., 2015). Additionally, GM and HGM are each associated with frequent genetic alterations (Matsubara et al., 2015). Therefore, the entity of HGM theoretically includes both congenital and reactive elements.

In conclusion, our data identified that in selected patients with DU who underwent biopsy or surgical resection, HGM was frequently observed around the ulcers, and *H. pylori* infection was significantly associated with the presence of HGM. Duodenal ulceration might be attributed to *H. pylori* infection of HGM. This new concept opens a new ambit to further investigate HGM in the duodenum and may lead to elucidation of a new ulceration mechanism.

Conflicts of interest and sources of funding. The authors declare that they have no conflicts of interest. No funding was received for this study.

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