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Hisataka Kobayashi, *Kyoto National Hospital*
Yukio Kajitani, *Kyoto National Hospital*
Takama Maekawa, *Kyoto National Hospital*
Tsuyoshi Itoh, *Kyoto National Hospital*
Rumi Murata, *Kyoto University*
Masaki Kanaoka, *Kyoto National Hospital*
Masao Naoki, *Kyoto National Hospital*
Hiroshi Satake, *Kyoto National Hospital*
Kochu Kogawa, *Kyoto National Hospital*
Junji Konishi, *Kyoto University*

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Hisataka Kobayashi, Yukio Kajitani, Takama Maekawa, Tsuyoshi Itoh, Rumi Murata, Masaki Kanaoka, Masao Naoki, Hiroshi Satake, Kochu Kogawa, and Junji Konishi

Abstract

Although a strong association has been established between chronic Helicobacter pylori infection and peptic ulcers, the role of H. pylori is not necessarily causative because there are many patients infected with H. pylori who do not develop peptic ulcer. Therefore, we studied the relationship between the gastric mucosal environment and the development of peptic ulcers. We examined 165 endoscopic biopsy specimens from the gastric mucosa of 33 patients with peptic ulcers using the 5-point gastric biopsy method. The follow-up biopsies done within 3 weeks were well correlated with the first biopsy samples. We also reviewed the clinicohistopathological findings of 2250 endoscopic biopsy specimens from 450 patients with active gastric and/or duodenal ulcers. Over 90% of the patients with duodenal ulcer, with or without gastric ulcer, had no fundic gland atrophy, and a high incidence of intestinal metaplasia and pyloric mucosal atrophy was found in the patients with gastric ulcer. These findings suggest that patients with concomitant active gastric and duodenal ulcers exhibit severe atrophic changes in the antral mucosa but not in the fundic mucosa.

KEYWORDS: peptic ulcer, endoscopy, biopsy, mucosal atrophy, intestinal metaplasia

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Histopathological Evaluation of Gastric Mucosal Environments in Peptic Ulcer Using the Endoscopic 5-Point Gastric Biopsy Method

Hisataka KOBAYASHI[a,b]*, Yukio KAJITANI[a], Takama MAEKAWA[a], Tsuyoshi ITOH[b,c], Rumi MURATA[d], Masaki KANAOKA[a], Masao NAOKI[a], Hiroshi SATAKE[a], Kochu KOGAWA[a] and Junji KONISHI[d]

Departments of [a]Gastroenterology, [b]Radiology and [c]Pathology, Kyoto National Hospital, Kyoto 612, Japan and [d]Department of Radiology and Nuclear Medicine, Kyoto University, Faculty of Medicine, Kyoto 606-01, Japan

Although a strong association has been established between chronic *Helicobacter pylori* infection and peptic ulcers, the role of *H. pylori* is not necessarily causative because there are many patients infected with *H. pylori* who do not develop peptic ulcer. Therefore, we studied the relationship between the gastric mucosal environment and the development of peptic ulcers. We examined 165 endoscopic biopsy specimens from the gastric mucosa of 33 patients with peptic ulcers using the 5-point gastric biopsy method. The follow-up biopsies done within 3 weeks were well correlated with the first biopsy samples. We also reviewed the clinicohistopathological findings of 2250 endoscopic biopsy specimens from 450 patients with active gastric and/or duodenal ulcers. Over 90% of the patients with duodenal ulcer, with or without gastric ulcer, had no fundic gland atrophy, and a high incidence of intestinal metaplasia and pyloric mucosal atrophy was found in the patients with gastric ulcer. These findings suggest that patients with concomitant active gastric and duodenal ulcers exhibit severe atrophic changes in the antral mucosa but not in the fundic mucosa.

Key words: peptic ulcer, endoscopy, biopsy, mucosal atrophy, intestinal metaplasia

Peptic ulcers are one of the most common gastrointestinal lesions. It is generally accepted that the pathogenesis of gastric mucosal damage, such as mucosal atrophy and metaplasia, and peptic ulcers are closely related to chronic *Helicobacter pylori* infection, especially chronic gastritis and duodenal ulcer (1, 2). Although almost all patients with peptic ulcer disease are infected with *H. pylori* (3), a large proportion of people who have no peptic ulcer, especially in Japan, are also infected with *H. pylori* (4, 5). Many authors have already reported factors which contribute to the development of peptic ulcer disease other than *H. pylori*, including the secretion of gastric acid and bicarbonate (6), the mucosal defensive effects of local hormones (7-9) and gastric mucosal blood flow (10). To date, histological examination was done in only a few studies on the etiology of peptic ulcers (11-13). The endoscopic 5-point gastric biopsy method (5PBM) is very useful for investigating the gastric mucosal environment histologically. 5PBM is an easy and repeatable method which can be used to clearly demonstrate atrophy and inflammatory changes of the gastric gland and metaplasic changes of the foveolar layer of the mucosa (11). Serial histological sections of the gastric mucosa in 33 patients with peptic ulcers were studied prospectively and retrospectively using 5PBM along with the clinicohistopathological findings for 450 patients with active gastric and/or duodenal ulcers.

Subjects and Methods

Patients. Thirty-three patients with active peptic ulcers were included in the study. Informed consent was obtained from all patients after the nature of the study was fully explained. A second 5PBM was performed within 3 weeks of the first in order to confirm the reliability of the first biopsy. In addition, we examined 2,250 histopathological samples obtained from 324 patients with active gastric and/or duodenal ulcers and 126 healthy volunteers in the control group. The clinical

* To whom correspondence should be addressed.

Table I Clinical diagnosis and age distribution of patients

Group	Number of patients						
	Age (years)						
	< 29	30-39	40-49	50-59	60-69	70 <	Total
Group NP	30	13	18	24	19	22	126
Group GU	18	25	24	26	23	26	142
Group DU	18	22	31	36	15	7	129
Group GDU	4	6	11	23	7	2	53
Total	70	66	84	109	64	57	450

Group NP: Patients with minimal mucosal change only
Group GU: Patients with active gastric ulcer
Group DU: Patients with active duodenal ulcer
Group GDU: Patients with concomitant active gastric and active duodenal ulcer

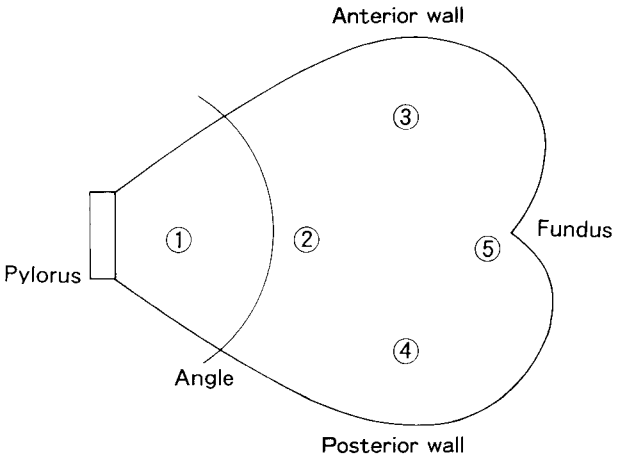

Fig. 1 The schema of stomach. Biopsy points: Site 1-Site 5

diagnosis and age distribution of all 450 subjects are shown in Table 1. Those 450 patients were selected from approximately 3,000 patients who had undergone endoscopic biopsy at the Gastroenterology Division, Kyoto National Hospital from 1977 to 1990. Patients from this sample of 3,000 were excluded if they had cancer, polyp, peptic ulcer scars alone, benign or malignant submucosal tumor, granulomatous gastritis (*i.e.*, sarcoidosis, syphilis, tuberculosis, fungus infection), malignant lymphoma or esophageal diseases. We also omitted the patients who could not be finally diagnosed and from whom the biopsy specimens were not adequate for evaluating mucosal atrophy. In all the patients chosen, active gastric and/or duodenal ulcer had been diagnosed based on the surgical or clinical findings.

The patients were divided into the following four groups: group NP, patients with minimal mucosal change ($n = 126$); group GU, patients with active gastric ulcer ($n = 142$); group DU, patients with active duodenal ulcer ($n = 129$); and group GDU ($n = 53$), patients with active gastric and duodenal ulcer.

Endoscopic biopsy procedure. The biopsy specimens for 5PBM histological examination were obtained from the following five specific sites of the stomach (Fig. 1). The first specimen (site 1) was obtained from the lesser curvature of the antrum; the second specimen (site 2) was obtained from the lesser curvature of the lower body; the third specimen (site 3) was obtained from the center of the anterior wall of the middle body; the fourth specimen (site 4) was obtained from the center of the posterior wall of the middle body; and the fifth specimen (site 5) was obtained from the lesser curvature of the upper body directly below the esophagogastric junction.

To assess the reliability of the 5PBM test, 165 specimens initially obtained from a group of 33 patients were compared with 165 biopsy specimens obtained from the same patients within 3 weeks.

Histological procedure. Tissue specimens were embedded in paraffin after fixation in a solution of 10 % formalin. The sliced sections were stained with hematoxylin and eosin. Tissue sections demonstrating goblet and/or Paneth's cells at the foveola gastrica or the gastric gland were histologically classified as intestinal metaplasia; tissues specimens showing discontinuity of the pyloric glands in the mucosa of site 1 and a fundal glandular layer thinner than the foveola gastrica layer (sites 2-5) were histologically classified as gastric gland atrophy (Fig. 2).

Statistical analysis. Differences between groups in the incidences of intestinal metaplasia and mucosal atrophy in the specimens obtained from the same sites of the gastric mucosa from the patients in the same decade of life were analyzed using the χ^2 test of the binomial distribution.

Results

Reliability of 5PBM. Of the 165 samples,

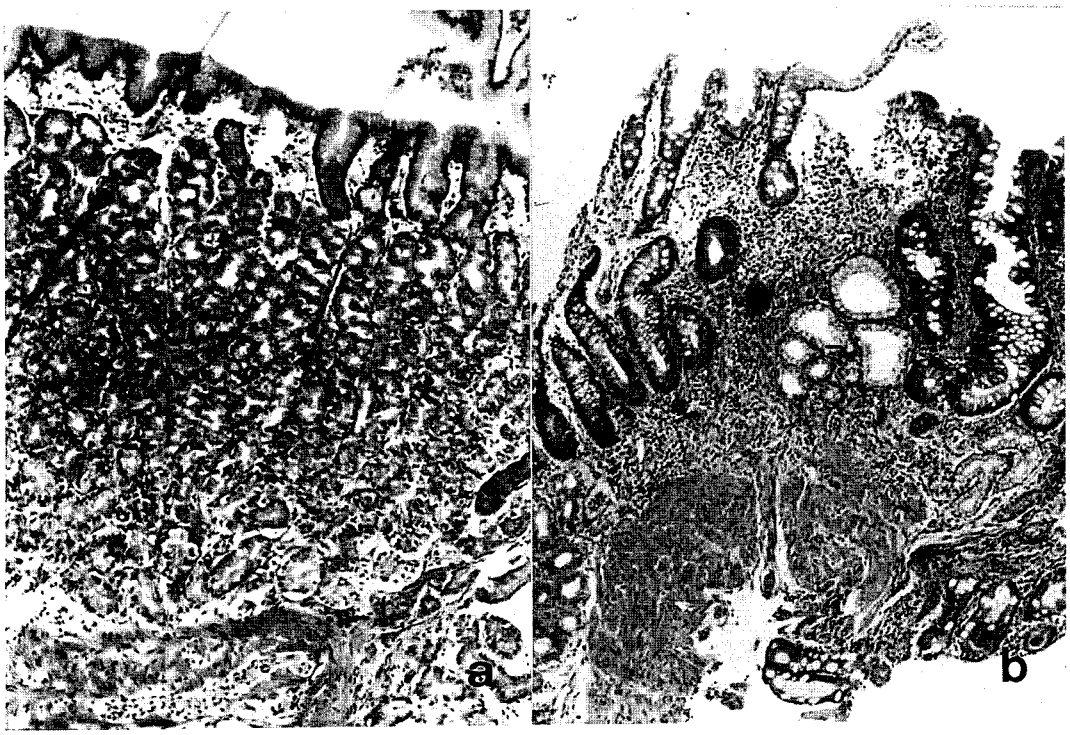

Fig. 2 Microscopic view of biopsy specimen. **a**) A section without atrophy and intestinal metaplasia; **b**) A section with severe mucosal atrophy and intestinal metaplasia. (× 20).

Table 2 Comparison of results from the first and the second 5PBMs examinations of the same patient performed within three weeks

Histological indication	Number of patients[a]			
	Scores (1st biopsy/2nd biopsy)			
	+/+	+/−	−/+	−/−
Intestinal metaplasia	87	17	14	47
Severe atrophy	84	8	8	65

[a]Total number of patients examined: 165.

the results with regard to intestinal metaplasia (+ or −) between the first and second biopsies agreed in 134 (81.2 %) samples. With regard to severe mucosal atrophy, 149 samples (90.3 %) showed concordant results between the first and second biopsies (Table 2).

Incidence of intestinal metaplasia and mucosal atrophy according to age and disease. In group NP patients, the incidence of severe gastric mucosal atrophy and of intestinal metaplasia at sites 1, 2, and 5 increased in those patients aged 30 years or older, but even in patients over 59 years, 50 % of these showed neither severe atrophy nor intestinal metaplasia. The incidences of severe atrophy and intestinal metaplasia at sites 3 and 4 were increased in all patients aged 40 or older (Table 3).

Differences of the incidence of mucosal atrophy and intestinal metaplasia. The incidences of severe gastric mucosal atrophy and intestinal metaplasia were significantly higher in group GU than in the NP patients aged ≤ 49 years for all sites examined ($P < 0.01$). That in group DU was significantly lower than in the NP patients aged ≥ 50 for all sites ($P < 0.01$). In addition, the incidences of severe gastric mucosal atrophy and intestinal metaplasia were significantly lower in group DU than that in group GU for the same age groups for all sites ($P < 0.01$).

In groups GDU and GU, the incidence of severe gastric mucosal atrophy and intestinal metaplasia in the antrum (site 1) was significantly higher than that in group

Table 3 Percentages of mucosal atrophy and intestinal metaplasia of pyloric (site 1) or fundic gland (site 2-5)

Age	Group	Mucosal atrophy					Intestinal metaplasia				
		1	2	3	4	5	1	2	3	4	5
29≥	NP	0	12.0	0	0	11.5	3.3	3.3	0	0	0
	DU	0	31.2	0	0	0	0	0	0	0	0
	GU	50.0††	56.2†	17.6††	20.0††	28.6	44.4†	16.7	5.9	5.9	11.1
	GDU	50.0	66.7	0	0	33.3	0	0	25.0	0	0
39≥, ≥30	NP	16.7	27.2	0	9.1	22.2	7.7	15.4	0	0	16.7
	DU	0	16.7	0	5.3	10.5	9.1	9.1	0	0	9.1
	GU	57.1††	61.9	36.0††	26.1	42.9	45.8††	40.0	16.0	8.0	16.0
	GDU	33.3	50.0	0	0	25.0	16.7	16.7	0	0	33.3
49≥, ≥40	NP	26.7	23.1	16.7	18.8	16.7	33.3	29.4	5.6	11.1	5.6
	DU	24.0	31.8	13.8	16.0	13.0	29.0	19.4	3.2	3.2	6.9
	GU	52.4	57.1††	47.6††	45.5	47.6††	75.0†	58.3	50.0†	41.7††	47.8†
	GDU	60.0	57.1	22.2	30.0	28.6	72.7††	36.4	9.1	9.1	10.0
59≥, ≥50	NP	41.7	59.1	33.3	54.2	50.0	66.7	66.7	25.0	37.5	50.0
	DU	20.0	32.1††	9.1††	6.5†	24.2†	41.6††	25.0††	8.3	8.3†	16.7†
	GU	70.8	77.3	37.5	43.5	48.0	73.1	50.0	30.8	23.1	38.5
	GDU	52.9	61.1	9.5	10.0†	28.6	52.2	34.8	8.7	13.0	34.8
69≥, ≥60	NP	56.2	57.9	56.3	41.2	62.5	57.9	42.1	47.4	21.1	55.6
	DU	16.7††	38.5	6.7†	7.1††	38.5	26.7††	20.0	6.7†	20.0	20.0††
	GU	80.0	84.2	36.4	33.3	57.1	78.3	47.8	21.7	17.4	40.9
	GDU	20.0	28.6	0††	14.3	50.0	57.1	28.6	0††	28.6	28.6
70≤	NP	52.4	60.0	50.0	38.1	57.1	63.6	50.0	50.0	27.3	47.6
	DU	0	0††	0††	0	33.3	40.0	0††	0††	0	20.0
	GU	79.2††	69.6	45.8	54.2	54.2	69.2	57.7	42.3	42.3	52.0
	GDU	50.0	50.0	0	0	0	50.0	0	0	0	0

†$P < 0.01$ to NP; ††$P < 0.05$ significantly different from NP, by χ^2 test. Abbreviations: See Table 1.

Table 4 Percentages of mucosal atrophy and intestinal metaplasia of pyloric (site 1) or fundic gland (site 3 + 4)

Age	Group	Mucosal atrophy		Intestinal metaplasia	
		Site 1	Site 3 + 4	Site 1	Site 3 + 4
49≥	NP	13.0	6.3	13.1	2.5
	DU	12.8	7.2	15.5	1.4
	GU	53.4†*	33.3†*	56.1†*	22.7†*
50≤	NP	49.2	45.2	63.1	34.6
	DU	17.1†	6.5†	37.9†	8.6†
	GU	76.5*	42.0*	73.3*	31.8*
	GDU	40.9**§	9.1†§	53.3§	11.7†§

†$P < 0.01$ to NP; *$P < 0.01$ to DU; **$P < 0.05$ to DU; §$P < 0.01$ to GU by χ^2 test. Abbreviations: See Table 1.

DU, while in groups GDU and DU the incidence of similar manifestations was significantly lower in the region of the fundic gland (sites 3 and 4) than that in groups NP and GU (Table 4).

Discussion

Acid secretion (14, 15), the bicarbonate barrier (6), local hormones (7-9), mucosal blood circulation (10), and various other factors which were added to the infection of *H. pylori* (1), have recently been reported to affect formation of peptic ulcers. However, few researchers have histopathologically investigated the relationship between the development of peptic ulcers and the gastric mucosal

environment, *i.e.*, the mucosal changes associated with chronic gastritis caused by *H. pylori* infection. Furthermore, in some of these studies, the gastric mucosal environment was investigated using the indirect methods of Congo red and methylene blue staining (16-18).

No severe atrophic changes were observed in the mucosa of the fundic gland in most patients with active duodenal ulcers independently of the presence or absence of active gastric ulcers even though the proportion of parietal cells is thought to be larger at sites 3 and 4. This finding indicates that the parietal cell mass is well maintained in patients with active duodenal ulcers. This supposition is consistent with the fact that the acidity of the gastric juice in many patients with active duodenal ulcers (with or without gastric ulcers) is higher than in patients without active duodenal ulcers (14, 15).

The results of the present study suggest that the gastric mucosal damage caused by chronic gastritis and aging which were closely related to *H. pylori* infection contributes to the development of gastric mucosal atrophy and intestinal metaplasia. Therefore, it is proposed that histological evidence of gastric mucosal atrophy and intestinal metaplasia on all or part of the mucosa is indicative of a greater susceptibility to the development of active gastric ulcer (12, 13).

In groups GDU and GU, the incidence of severe gastric mucosal atrophy and intestinal metaplasia at the antrum (sites 1 and 2) was quite high. However, the incidence of severe gastric mucosal atrophy of the region of the fundic gland (sites 3 and 4) was very low in groups GDU and DU.

Considering these results, we propose that both high acid secretion (commonly associated with duodenal ulcers) and local mucosal damage (commonly associated with gastric ulcers) must be present in the stomach concurrently for concomitant active gastric/duodenal ulcers to develop. It seems reasonable to assume that *H. pylori* infection may relate to the mucosal changes associated with chronic gastritis and aging and that these changes can gradually progress to include the entire gastric mucosa. Therefore, only when injury to the fundic mucosa is mild and when this progressive gastric mucosal damage extends to the antral region and becomes severe are patients at increased risk for the development of concomitant active gastric and duodenal ulcers.

This hypothesis is consistent with the findings that many patients who exhibited both active gastric and duodenal ulcers were between 40 and 70 years old, and that many cases of gastric mucosal damage due to chronic gastritis and aging were progressing during this period. Furthermore, this finding is consistent with previous reports that most patients with active concomitant gastric and duodenal ulcers had the active gastric ulcers in the region of the antrum (14, 15). In the 53 patients in group GDU, only five ulcers (three solitary and two multiple) were found in fundic gland region. These findings are compatible with the hypothesis of the boundary line (19), because most of the patients in group GDU had the histological boundary line in the lower fundic region. Those investigators also reported that most of the active gastric ulcers were found near the anti-acidic side of the boundary line.

In conclusion, the findings of the present study suggest that the histopathological changes of the gastric mucosa are major contributing factors which were added to the effects of *H. pylori* in the etiology and localization of peptic ulcers.

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