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Pathological Assessment of the Contribution of *Helicobacter pylori* Infection to Perforated Duodenal Ulcer

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There is controversy concerning the contribution of *Helicobacter pylori* (*H. pylori*) to perforation by duodenal ulcers. We therefore investigated the association between the pathological findings and *H. pylori* infection in the 89 operated cases. We performed hematoxylin and eosin staining, Masson trichrome staining, and to observe the presence of *H. pylori* by immunohistochemical staining. We divided the cases into an acute ulcer perforation type (A group) and a chronic ulcer perforation type (C group). There were 60 cases in the C group and 29 cases in the A group. Infection was observed in the pyloric gland region in 81 cases without detection of *H. pylori* around the site of ulcer perforation. In the A group, 55% of the cases had up to 20 bacteria/gastric pit present in a few of gastric pits. However in the C group, 88% were almost all of or many gastric pits with more than 20 bacteria/gastric pits. Thus the infection was significantly higher in the C group than in the A group. The two groups differed significantly in level of *H. pylori* infection. The results suggested that the acute type and the chronic type differed in the mechanism that led from ulcer formation to perforation.

Key words: perforated duodenal ulcer, *Helicobacter pylori*, acute ulcer, chronic ulcer, immunohistochemical staining

Introduction

After *Helicobacter pylori* (*H. pylori*) was reported by Warren and Marshall in Australia in 1983[1)2)], it became clear that *H. pylori* contributes to the development of gastroduodenal ulcers. However, although the leaking roof hypothesis has been proposed by Goodwin[3)] and the gastrin link hypothesis by Levi et al[4)] to explain the pathogenetic mechanism of duodenal ulcers, they remain inadequate in many respects. Particularly because it is a condition that requires emergency treatment, the association between perforated duodenal ulcer with *H. pylori* has not been sufficiently investigated, and there is controversy in regard to the contribution of *H. pylori* to perforation[5)~11)].

Duodenal ulcer perforation does not always occur as the result of repeated chronic ulceration. Quite a few patients come to the hospital with what seems to be a sudden course without any past history or symptoms[12)]. Suzuki reported close associations between the macroscopic characteristics at surgery and both the pathological findings and the clinical course in perforated duodenal ulcer and, among other things, classified ulcer morphology into 3 types: a chronic peptic ulcer type, an acute exacerbation of chronic ulcer type, and an acute perforation type[13)]. Occasional reports that had classified perforated duodenal ulcers morphologically had been published in the past[14)], but few reports had gone so far as to perform a pathological study.

The treatment of perforated duodenal ulcer, especially its surgical treatment, has changed greatly over the past 20 years[12)]. Powerful gastric acid secretion inhibitors, i.e., H_2 receptor blockers and proton pump inhibitors, and antibiotic therapy to eradicate *H. pylori* have become available, and drug ther-

apy has been widely adopted. Thus, while gastrectomy, which is a curative operation for ulcers, was generally used to treat perforated duodenal ulcers in the past, selection of a less invasive operation, simple surgical closure of the perforation site, followed by drug therapy, has recently become the preferred treatment[12)15)~17)]. Moreover, when the peritonitis is not severe, conservative therapy by means of intragastric decompression, gastric acid secretion inhibitors, and antibiotics, without any surgical intervention, has come to be accepted[12)17)].

In the 1980s several 10s to 50 gastrectomies a year were performed for perforated duodenal ulcer in the Department of Surgery II of Tokyo Women's Medical University Hospital. However, only a few gastrectomies a year are performed in the Critical Care Medical Center of our hospital, which opened in 1989. This trend corresponds to the discovery of *H. pylori*, the dissemination of knowledge of its actions, and to the widespread availability of gastric acid secretion inhibitors. Because of this, it has become difficult to perform pathological studies of ulcer perforation sites in surgical specimens and to investigate associations with *H. pylori*.

We therefore pathologically examined perforated duodenal ulcers in pathology specimens from cases in which gastrectomy was performed to treat perforation in the past and investigated the association of *H. pylori* with the pathological findings.

Patients and Methods

Patients

The materials used in this study consisted of specimens from the 89 cases in which specimens that included the ulcer perforation site and pyloric gland region were available among the 179 cases in which gastrectomy was performed for perforated duodenal ulcer in the Department of Surgery II of our hospital between January 1981 and March 1989.

Clinical investigation

Information concerning age, gender, history of nonsteroidal anti-inflammatory drug (NSAID) use, smoking history, past history of gastroduodenal ulcer, presence and duration of symptoms before the perforation, and macroscopic findings at the perforation site during surgery was obtained from the hospital records. However, past history of gastroduodenal ulcer was judged on the basis of diagnosis by an upper gastrointestinal (GI) contrast series or upper GI endoscopic examination.

Pathological investigation

1) Morphological investigation of the ulcers

The paraffin-embedded surgical specimen of the duodenal ulcer perforation site was cut into thin sections (4 μm thick), and they were stained with Masson trichrome to detect fibrosis, an indicator of having become chronic, as well as by routine staining with hematoxylin and eosin (HE). The Masson trichrome specimens were evaluated for the presence and amount of fibrosis and scar formation around the ulcer, the presence of a 4-layer structure that is distinct in chronic ulcers (exudative layer, necrotic layer, granulation layer, cicatricial layer), the presence of deformity of the lamina muscularis propria by fibrosis, and the presence of arterial wall thickening and fibrosis around the ulcer. In addition, the HE specimens were evaluated for class of inflammatory cells infiltrating around the ulcer and for mucosal inflammation, edema, and capillary bleeding.

Based on the above morphological findings, the cases were divided into two types, an acute ulcer perforation type (A group) and a chronic ulcer perforation type (C group). Because fibrosis and scar formation were the most important findings for dividing two groups[18)], they were first divided according to fibrosis and scar formation around the ulcer into cases in which perforation was observed at a site where fibrosis was prominent and scar formation was present, and cases in which there was little fibrosis. The former were assigned to the C group, and an additional 5 items were evaluated in the latter (Table 1)[18)]. The cases in which 3 or more chronic findings were observed were assigned to the C group, and the cases in which 3 or more acute findings were observed were assigned to the A group. The clinical background of these two groups was investigated.

2) Investigation of *H. pylori* infection

Sections of the duodenal ulcer perforation site that included the pyloric gland region were immu-

Table 1 Pathomorphological factors and acute and chronic findings

Pathomorphological factors	Acute findings	Chronic findings
4-layer structure of the ulcer base	Indistinct	Distinct
Lamina muscularis propria	No deformity, ruptures	Deformity caused by fibrosis
Arterial wall thickening and fibrosis around the ulcer	No	Yes
Type and degree of infiltrating inflammatory cells	Neutrophil-predominant	Lymphocyte-predominant
Mucosal inflammation, edema, and capillary bleeding	Yes	No

Table 2 Comparison between the clinical background of the 2 groups

Characteristics	Total (N = 89)	A group (N = 29)	C group (N = 60)	p-value
Age (years, range (median))	17-68 (31.0)	18-57 (32.0)	17-68 (30.5)	NS
Gender (Male/Female)	86/3	28/1	58/2	NS
				no. (%)
History of NSAID use	2 (2)	1 (3)	1 (2)	NS
Smoking	73 (82)	25 (86)	48 (80)	NS
Past history of ulcer	29 (33)	4 (14)	25 (42)	$p < 0.01$
Symptoms a week or more before perforation	29 (33)	4 (14)	25 (42)	$p < 0.01$
Macroscopic findings at surgery				
Kissing ulcer	18 (20)	5 (17)	13 (22)	NS
Punched out	9 (10)	7 (24)	2 (3)	$p < 0.01$
Adhesion, deformity, scar, pocket formation	13 (15)	0 (0)	13 (22)	$p < 0.01$

nohistochemically stained by the indirect enzyme antibody method. Anti *H. pylori* rabbit polyclonal antibody (DAKO) was used as the primary antibody, and after reacting with the secondary antibody and peroxidase-labeled rabbit immunoglobulin, a color reaction was achieved with diaminobenzidine to which hydrogen peroxide had been added.

The area around the site of duodenal ulcer perforation was examined with a microscope for the presence of *H. pylori*, and the level of *H. pylori* infection was qualitatively evaluated based on the number of *H. pylori* bacteria in the epithelial layer of the mucosa. The method described by Satoh et al[19] was used to make the qualitative evaluation on the following 4-level scale: level 0, null; level 1, a small number of bacteria (up to 20/gastric pit) present in a few of gastric pits; level 2, a large number of bacteria (more than 20/gastric pit) present in several gastric pits or a small number of bacteria present in many gastric pits; level 3, a large number of bacteria present in nearly all of gastric pits. We then assessed the *H. pylori* infection level and morphological findings and investigated the association between the A group and C group and the *H. pylori* infection level.

Statistical analysis

The Mann-Whitney *U*-test was used for the statistical analysis of age. The χ^2-test and Fisher's exact test (when the individual value in any cell was less than five) were used for the other statistical analyses. A p value <0.01 was considered evidence of statistical significance.

Results

1. Clinical investigation

The mean age of the subjects was 35.0 years. According to gender, there were 86 males and 3 females. There were 2 subjects (2%) with a history of taking NSAIDs and 73 (82%) with a history of smoking. There were 29 subjects (33%) with a past history of ulcer, and 29 (33%) had symptoms for a week or more before the perforation. The macroscopic findings at surgery consisted of kissing ulcers in 18 cases (20%), a punched out appearance in 9 cases (10%), adhesion, deformity, scar formation, and pocket formation in 13 cases (15%) (Table 2).

2. Pathological investigation

1) Morphological investigation of the ulcers

Examination for fibrosis and scar formation around the ulcer revealed marked fibrosis and perforation at the site of scar formation 41 cases (46%), and little fibrosis or scar formation in 48 cases (54%). Among the latter cases, 3 or more chronic findings were present in 19 cases, and when they were added to the 41 cases in which marked fibrosis was observed, the total number of cases in the chronic ulcer perforation group (C group) increased to 60 (67%). By contrast, the acute ulcer perforation group (A group), in which there was little fibrosis and 3 or more acute findings were present, consisted of 29 cases (33%) (Fig. 1).

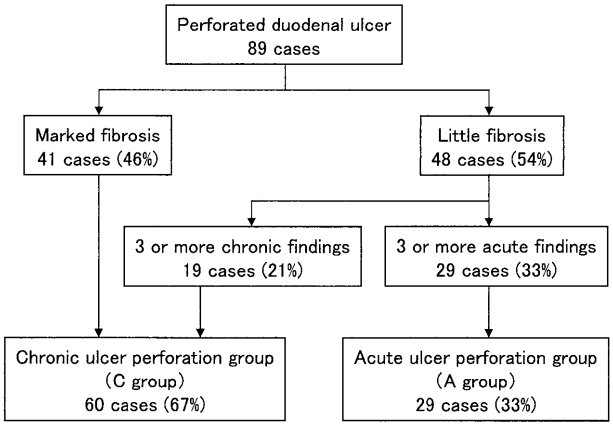


Fig. 1 Chronic ulcer perforation group and acute ulcer perforation group

The morphological findings in the two groups (Figs. 2 and 3) revealed a distinct 4-layer structure (Fig. 2-3) in the chronic ulcers in 87% in the C group and 48% in the A group. Deformity of the lamina muscularis propria by fibrosis (Fig. 2-1 and 2) was observed in 77% of the C group and in 17% of the A group, and arterial wall thickening and fibrosis around the ulcer (Fig. 2-4) was observed in 88% of those in the C group and 17% of those in the A group. By contrast, neutrophil-predominant inflammatory cell infiltration (Fig. 3-3), which is a characteristic finding of acute inflammation, was observed in 76% of the A group and 17% of the C group. In addition, mucosal inflammation, edema, and capillary bleeding (Fig. 3-4) was noted in 100% in the A group and 27% in the C group (Table 3).

Median age at the onset of symptoms was 32.0 years in the A group and 30.5 years in the C group (Fig. 4). The male to female ratio was 28 : 1 in the A group and 58 : 2 in the C group. One subject in both groups had a history of taking NSAIDs. There were 25 subjects (86%) in the A group with a history of smoking, and 48 (80%) in the C group. There were 4 subjects (14%) in the A group with an ulcer history who experienced symptoms a week or more before the perforation, and 25 (42%) in the C group. The macroscopic findings at surgery showed kissing ulcers in 5 subjects (17%) in the A group and 13 subjects (22%) in the C group. There was a punched out appearance in 7 subjects (24%) in the A group and 2 subjects (3%) in the C group, and adhesions, deformity, scar formation, and pocket formation were observed in 0 subjects (0%) in the A group and 13 subjects (22%) in the C group (Table 2).

2) Investigation of *H. pylori* infection

H. pylori was not observed around the duodenal ulcer perforation in the specimens we examined in any of the cases. Infection was observed in the pyloric gland region in 81 cases (91%). It was level 1 in 20 cases (22%), level 2 in 35 cases (40%), and level 3 in 26 cases (29%) (Figs. 5 and 6).

The positive rates for morphological findings will be described according to *H. pylori* infection level. Fibrosis or scar formation was observed in 38% at level 0, 15% at level 1, 51% at level 2, and 65% at level 3. The 4-layer structure in the ulcer base was observed in 50% at level 0 and 55% at level 1, as opposed to 86% at level 2 and 81% at level 3. Deformity of the lamina muscularis propria was noted in 50% at level 0, 35% at level 1, 63% at level 2, and 69% at level 3. Arterial wall thickening and fibrosis around the ulcer was observed in 25% at level 0 and 30% at level 1, as opposed to 83% at level 2 and 81% at level 3 (Fig. 7). By contrast, neutrophil-predominant inflammatory cell infiltration, which is a characteristic finding of acute inflammation, was observed in 75% at level 0 and 60% at level 1, as opposed to 29% at level 2 and 15% at level 3. In a similar manner, even mucosal inflammation, edema, and capillary bleeding were observed in 88% at level 0 and 80% at level 1, as opposed to 49% at level 2 and only 19% at level 3 (Fig. 8).

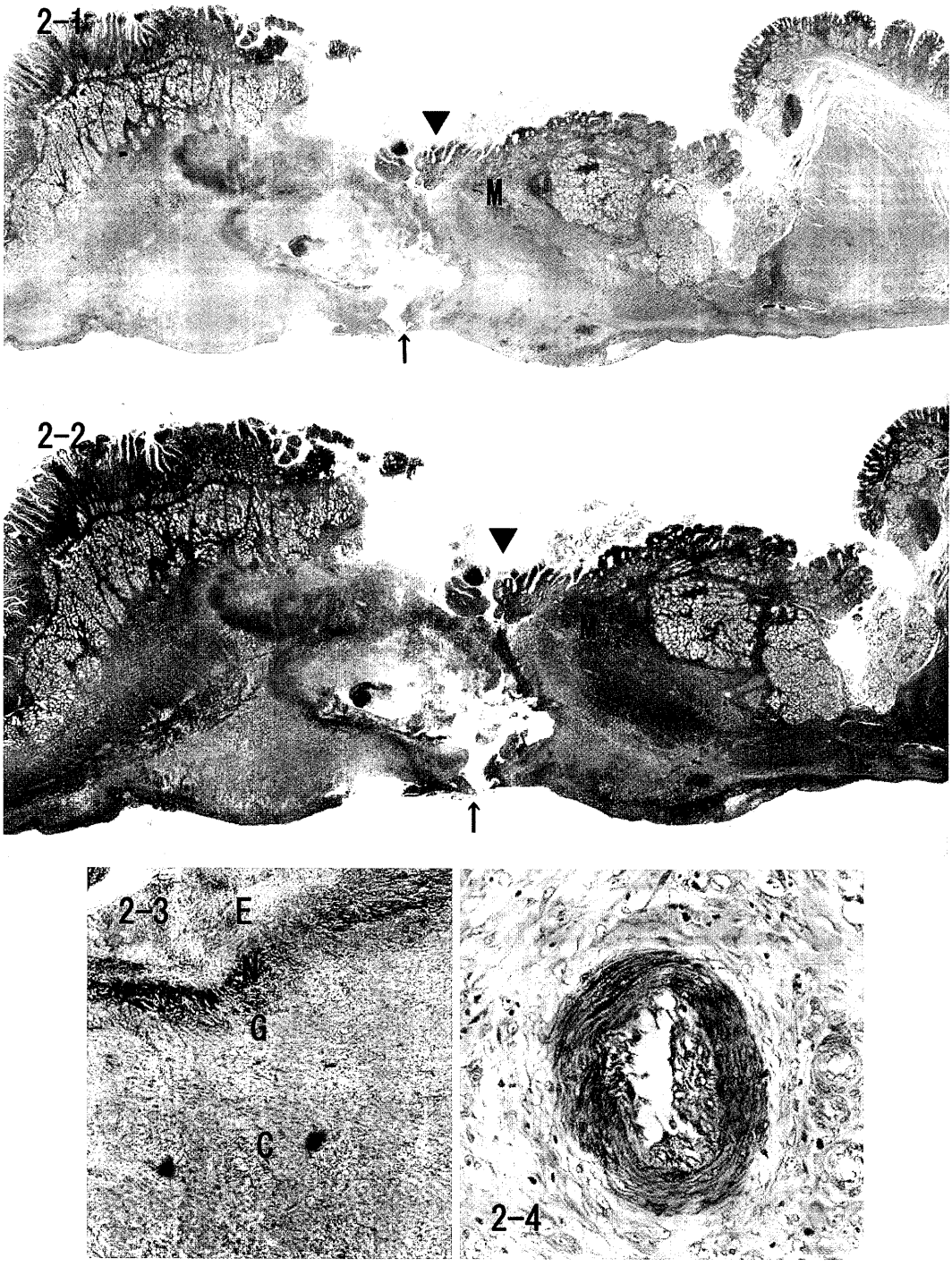
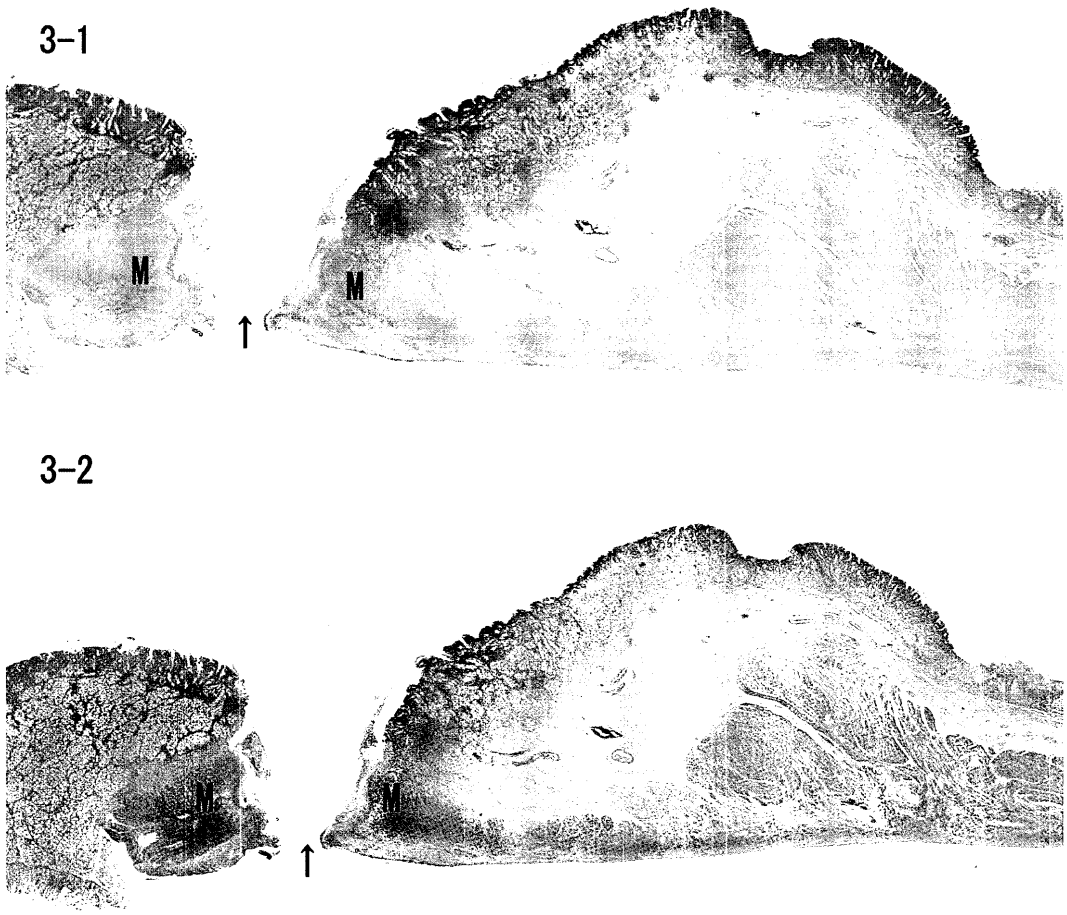


Fig. 2 Pathomorphological findings in the chronic ulcer perforation group (C group)
2-1: Marked fibrosis is seen around the perforation site (↑). Acinar formation (▼) of regenerating epithelium is observed in mucosa around ulcer. The lamina muscularis propria has been deformed by fibrosis (M). (HE staining, loupe view)
2-2: Fibrosis is clearly stained blue and the lamina muscularis propria red in this Masson trichrome specimen. (Masson trichrome specimen, loupe view)
2-3: The 4-layer structure of the ulcer base can be seen. Exudative layer (E), necrotic layer (N), granulation layer (G), and cicatricial layer (C). (Masson trichrome specimen, ×40)
2-4: Arterial wall thickening and fibrosis are seen. (Masson trichrome specimen, ×200)



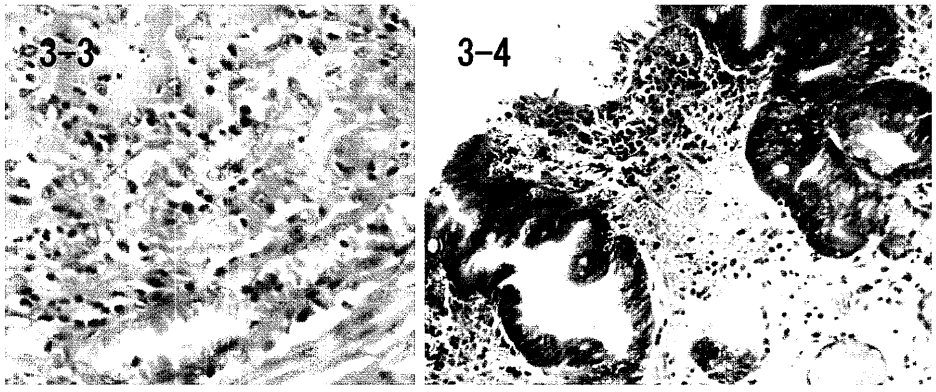


Fig. 3 Pathomorphological findings in the acute ulcer perforation group (A group)
3-1: Hardly any fibrosis is seen, including around the perforation (↑). The lamina muscularis propria has been ruptured by the ulcer margin (M). (HE specimen, loupe view)
3-2: Hardly any blue, which indicates fibrosis, is observed in the Masson trichrome specimen. (Masson trichrome specimen, loupe view)
3-3: An inflammatory picture is seen in the submucosal layer. Neutrophil transition from the blood vessel to tissue is observed. (HE specimen, ×400)
3-4: An inflammatory picture is seen in the mucosa. Neutrophil-predominant inflammatory cell infiltration and capillary bleeding are observed. (HE specimen, ×200)

Comparison of *H. pylori* infection between the groups revealed that in the A group there were 5 level 0 cases (17%), 16 level 1 cases (55%), 6 level 2 cases (21%), and 2 level 3 cases (7%), whereas in the C group, there were 3 level 0 cases (5%), 4 level 1 cases (7%), 29 level 2 cases (48%), and 24 level

Table 3 Comparison between the pathomorphological findings in the 2 groups

Pathomorphological factors	A group (N = 29)	C group (N = 60)	Total (N = 89)
Chronic findings			no. (%)
4-layer structure of the ulcer base	14 (48)	52 (87)	66 (74)
Deformity of the lamina muscularis propria	5 (17)	46 (77)	51 (57)
Arterial wall thickening and fibrosis around the ulcer	5 (17)	53 (88)	58 (65)
Acute findings			
Neutrophil-predominant inflammatory cell infiltration	22 (76)	10 (17)	32 (36)
Mucosal inflammation, edema, capillary bleeding	29 (100)	16 (27)	45 (51)

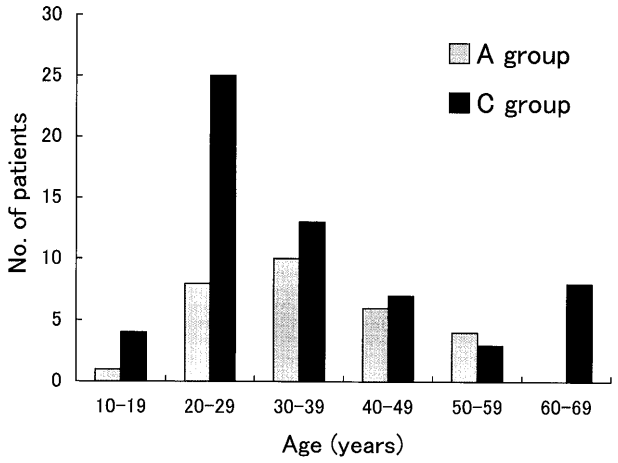


Fig. 4 Comparison between age at onset in the 2 groups

3 cases (40%) (Fig. 9).

Discussion

H. pylori is now thought to play a major role in the etiology of duodenal ulcer[20]. However, there is controversy about the role of *H. pylori* in the process of ulcer formation as shown by the leaking roof hypothesis proposed by Goodwin[3]and the gastrin link hypothesis proposed by Levi et al[4]. There is also the difficulty of investigating perforated duodenal ulcers, which are important in the surgical and emergency areas, and the mechanism responsible for the occurrence of perforation has not been clarified. Nor is it clear whether U1-IV ulcers simply progress and perforate, or whether there is some special factor that when added to the ulcer leads to perforation. There is also controversy in regard to the contribution of *H. pylori*[5)~11)]. The authors therefore first investigated the clinical characteristics of perforated duodenal ulcers, and then added a pathological investigation and assessed the contribution by *H. pylori*.

1. Clinical investigation

The mean age of the patients who were the subjects of this study was 35.0 years. It has been reported that many duodenal ulcer perforation patients in Japan are relatively young, with a peak age in the 3rd to 4th decade[14)21)22)], whereas in other countries many patients are middle aged or older, or elderly[5)16)23)]. It has also been reported that there is a tendency for perforated duodenal ulcer to increase with age in elderly persons 70 years of age and older in Japan as well[24)]. The peak age in our own study was also in the 3rd decade, but there were occasional patients 60 years of age and older.

According to gender, males predominated (86 patients, 97%), and females accounted for a mere 3%. The proportion of females in Japan has been reported to be 3-7%[6)14)21)], and the results were almost the same in our own study. Sufficient research has not yet been conducted to determine the reason for the greater numbers of males.

The NSAIDs currently being widely used are said to be a major cause of ulcer formation together with *H. pylori*. There are reports that NSAIDs are the cause of perforation[25)] as well as reports that NSAIDs are a more important independent factor in ulcer perforation than *H. pylori*[26)]. By contrast, there are also reports that NSAIDs contribute little to the perforation of duodenal ulcers[6)8)]. In our own case series only 2 patients (2%) were found to have taken NSAIDs, and it was impossible to clearly link ulcer perforation and NSAIDs.

There have been many reports that smoking is an important risk factor for ulcer perforation even

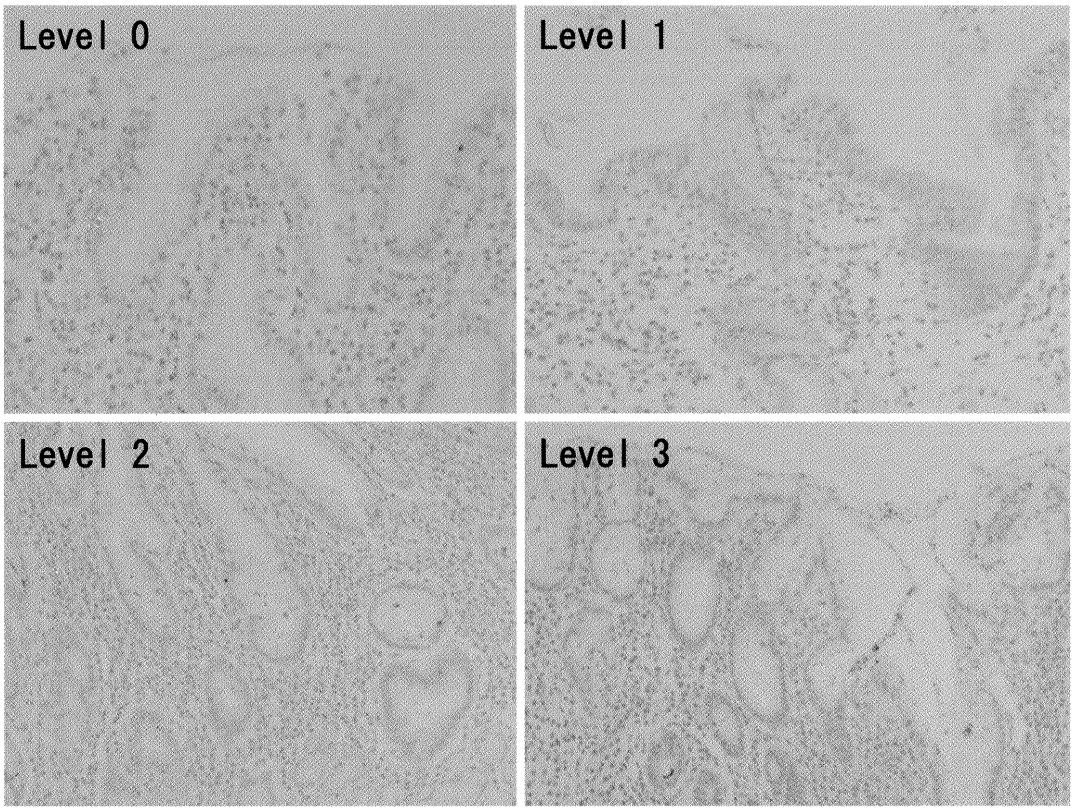


Fig. 5 Immunohistochemical staining for *H. pylori* (×200)
Level 0: null
Level 1: a small number of bacteria (up to 20/gastric pit) present in a few of gastric pits
Level 2: a large number of bacteria (more than 20/gastric pit) present in several gastric pits or a small number of bacteria present in many gastric pits
Level 3: a large number of bacteria present in nearly all of gastric pits

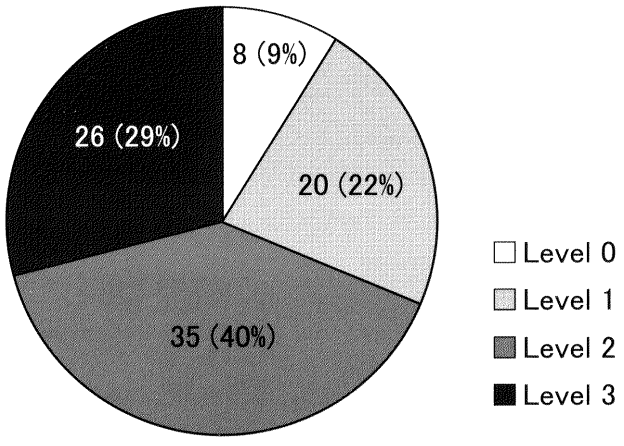


Fig. 6 Qualitative evaluation of *H. pylori* infection

after the discovery of *H. pylori*[26)27)], and it has been reported that 78-84% of duodenal ulcer perforation patients have a history of smoking[5)9)]. The smoking rate in our own study was almost the same, 82%, and tended to be higher than the smoking rate of approximately 70%[28)] among males in Japan in the 1980s.

There were 29 subjects (33%) with a history of ulcer, and there were 29 (33%) who had symptoms for a week or more before the perforation. It has been reported that 24-80% of duodenal ulcer perforation patients have a past history of ulcer[5)9)14)21)26)], but the definition of history of ulcer has varied with the study, e.g., according to whether there are digestive symptoms or whether there is a history of medication. Because the definition of history of ulcer in our own study was having had an ulcer that had been diagnosed morphologically by an upper GI series or by upper GI endoscopy, we suspect that there were fewer cases with a history of ulcer than in earlier studies in which history of ulcer was judged on the basis of symptoms alone. Moreover,

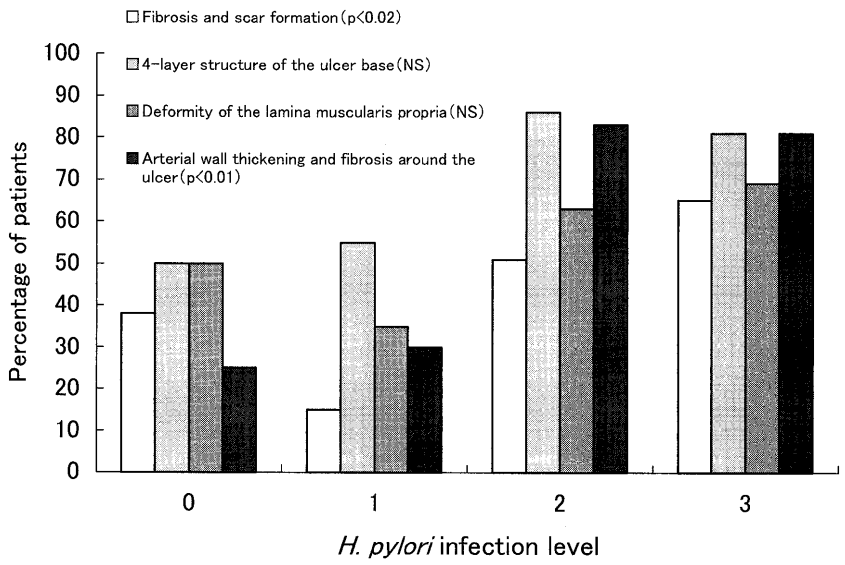


Fig. 7 Pathomorphological findings (chronic findings) and *H. pylori* infection level

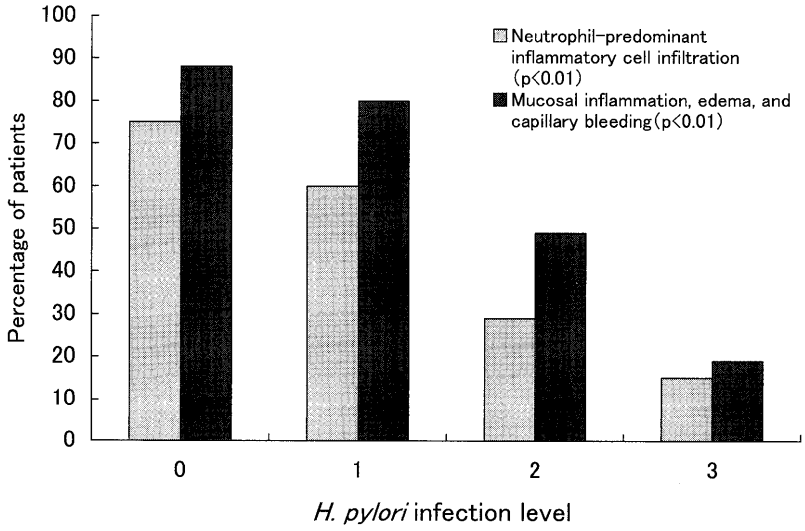


Fig. 8 Pathomorphological findings (acute findings) and *H. pylori* infection level

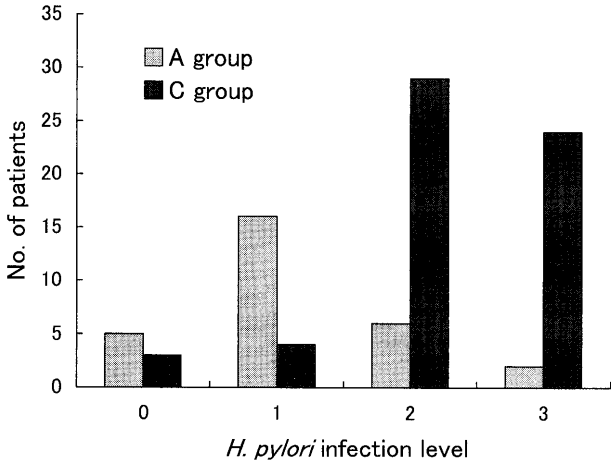


Fig. 9 Comparison of the *H. pylori* infection level between the 2 groups

there is a report in regard to symptoms that dyspepsia was experienced by 39% of patients for 3 months or more before the perforation[5], and while the duration is different, that finding was almost the same as in our own study.

There have been few reports of studies that have investigated the macroscopic findings at surgery. Nomura et al investigated 60 cases of perforated duodenal ulcer and reported multiple ulcers in 6 cases (10%), and that there were kissing ulcers in 2 (3%) of them[29]. Evidence of kissing ulcers was observed in 18 cases (20%) in our own study, and the rate tended to be higher.

2. Pathological investigation

1) Morphological investigation of the ulcers

There were 29 cases (33%) in the A group and 60 cases (67%) in the C group, and the ratio was almost 1 : 2. In the report by Kitajima et al[22], who used the Suzuki method[13] to classify the cases according to the macroscopic findings, there were 21 cases (34%) of the chronic peptic ulcer type, 22 cases (36%) of the acute exacerbation of chronic ulcer type, and 18 cases (30%) of the acute perforation type. If the acute perforation type is defined as the "acute group" and the chronic peptic ulcer type and acute exacerbation of chronic ulcer type combined as the "chronic type", the ratio of the acute group to the chronic group was 18 cases to 43 cases, or 1 : 2.4, and tended to be almost the same as in our study. Moreover, in reports that evaluated "acute" and "chronic" based on the clinical course, Taylor et al[30] reported an acute group to chronic group ratio of 79 cases to 177 cases (1 : 2.2), and Boey et al[23] reported a ratio of 60 cases to 132 cases (1 : 2.2), both of which were close to the ratio in our pathology study, even though no pathological evaluations had been performed.

Examination of the clinical characteristics in each of the groups revealed no significant differences between them in age, gender, history of taking NSAIDs, or history of smoking. Nevertheless, there were more younger subjects in the A group, in which the peak age was in the 4th decade, than in the C group, which tended to have 2 peaks, one in the 3rd decade and the other in the 7th decade. All of the patients who were 60 years of age or older were in the C group. In the report by Kitajima et al[22] the peak in both the acute group and chronic group was in the 3rd decade. In that report there was 1 patient (17%) 60 years of age or over in the acute group and 5 patients (83%) 60 years of age or over in the chronic group, and thus they were more numerous in the chronic group than any other age group which tended to be the same as in our own study.

By contrast, Watanabe et al[24] investigated peptic ulcer perforation pathologically in patients 70 years of age and over and reported the chronic peptic ulcer type in 9 cases (45%), the acute exacerbation of chronic ulcer type in 4 cases (20%), and the acute perforation type in 7 cases (35%), and the percentages of all age groups in the acute group in our study and Kitajima's study (33, 30%) tended to be the same. At least the percentage of acute ulcer perforation appeared not to be high in the elderly.

Significantly more of those in the C group had a past history of ulcer and symptoms a week or more before the perforation. This is thought to show consistency between the morphological findings of chronic ulcer perforation and the clinical course.

Examination of the macroscopic findings at surgery revealed significantly more cases with a punched out appearance in the A group and significantly more cases with adhesions, deformity, scar formation, and pocket formation in the C group, suggesting consistency between the macroscopic findings at surgery and the pathological findings.

2) Investigation of *H. pylori* infection

In our study, *H. pylori* was not observed around the site of duodenal ulcer perforation in the specimens we examined in any of the cases. Only one report was found it showed the presence of *H. pylori* in the perforated duodenal ulcer wall[31]. It has been said that the principal site of *H. pylori* infection is the gastric mucosa and that it does not infect the duodenal mucosa[20]. Goodwin[3] have hypothesized that ulcers are formed by *H. pylori* colonizing gastric metaplasia of the duodenum. The subjects of our study were patients with ulcer perforation, and although we were unable to judge, because we did not study unperforated ulcers, it seemed that gastric metaplasia colonized by *H. pylori* may have been lost in the process of ulcer formation or perforation.

On the other hand, *H. pylori* infection in the pyloric gland region was observed in 81 cases (91%). The duodenal ulcer *H. pylori* infection rates in reports by other investigators are approximately 90%[32], and consistent with our own study. Nevertheless, reports of *H. pylori* infection rates in perforated duodenal ulcers have ranged from 42% to 92%[5)6)8)~10)31)], and this is one of the reasons for the controversy about the association between *H. pylori*

and perforated duodenal ulcer.

Sakakibara et al investigated *H. pylori* infection qualitatively by an evaluation method similar to our own and reported finding that *H. pylori* infection of duodenal ulcers was level 0 in 12%, level 1 in 33%, and levels 2 and 3 in 55%[32]. Our own results: level 0 in 10%, level 1 in 22%, and levels 2 and 3 in 69% showed a very similar tendency.

Examination of the association between the morphological findings and the two groups showed that the positive rates for chronic ulcer findings, i.e., fibrosis and scar formation, a distinct 4-layer structure at the base of the ulcer, deformity of the lamina muscularis propria, and arterial wall thickening and fibrosis around the ulcer, tended to rise with the level of *H. pylori* infection. However, the significant difference in fibrosis and scar formation was $p < 0.02$, and no significant differences were observed in distinct 4-layer structure or deformity of the lamina muscularis propria. By contrast, the percentages positive for the findings of neutrophil-predominant inflammatory cell infiltration, mucosal inflammation, edema, and capillary bleeding were found to tend decline with the level of *H. pylori* infection, and significant differences were found in all of them.

The associations between the individual groups and *H. pylori* infection showed that there were 21 cases (72%) of levels 0 and 1 in the A group, but only 8 cases (28%) of levels 2 and 3, whereas in the C group there were 53 (88%) level 2 and 3 cases, and they accounted for the majority. The infection level was low in the A group and tended to be high in the C group, and the difference between the groups was significant. The *H. pylori* infection rate in the A group was 83%, and it was not lower than in reports by other investigators, however, qualitatively there were 16 (55%) level 1 cases, accounting for approximately half, suggesting a lower contribution to ulcer formation than in the C group. On the other hand, approximately 90% of the cases in the C group, were level 2 and 3, and heavy *H. pylori* infection was observed. The C group was characterized by a pathological picture of chronic ulcer breakdown, and it was suggested that *H. pylori*, the principal cause of chronic ulcers, played an important role.

NSAIDs are said to be an important factor in ulcer formation in *H. pylori*-negative ulcers, and there are also reports that NSAIDs play an important role in perforation as well[26)27)]. The *H. pylori*-negative rate in the A group was 17%, but only 2 subjects in this study had a history of taking NSAIDs, and the contribution of NSAIDs to ulcer perforation was unclear. Thus, the role that *H. pylori* plays in the pathogenetic mechanism of perforation in the two groups differs, and the results suggest that some factor other than *H. pylori* infection and NSAIDs contributes to the development of perforation, particularly to acute ulcer perforation.

Various factors have been pointed to as leading to ulcer perforation[22], but the mechanism has not been adequately elucidated. Our study showed that the level of *H. pylori* infection in perforated duodenal ulcer patients differs according to acute and chronic pathomorphological differences. It appears that in the future it will be necessary to elucidate the mechanism of ulcer perforation based on the pathomorphological aspects.

Conclusion

We used material from cases of perforated duodenal ulcer treated by gastrectomy to investigate an association between the pathomorphological findings and *H. pylori* infection. There was a significant difference in the level of *H. pylori* infection between the acute ulcer perforation group and the chronic ulcer perforation group as well as differences in clinical background. The mechanism that leads from ulcer formation to perforation is inferred to differ in the acute type and the chronic type. The results suggested that there are other factors that cause perforation in addition to *H. pylori*, particularly in the acute ulcer perforation cases.

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穿孔性十二指腸潰瘍における *Helicobacter pylori* 感染の関与に関する病理学的検討

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現在，十二指腸潰瘍と *Helicobacter pylori*（*H. pylori*）の関連が明らかにされているが，十二指腸潰瘍の穿孔に対する *H. pylori* の関与については議論が分かれている．そこで，1981年1月～1989年3月に当院第二外科で行われた179例の穿孔性十二指腸潰瘍に対する胃切除手術症例のうち，潰瘍穿孔部と幽門腺領域の標本が存在する89例につき，病理形態学的所見と *H. pylori* との関連について検討した．ヘマトキシリン・エオジン染色，マッソン・トリクローム染色を行い，病理形態学的所見により急性潰瘍穿孔型（A群）と慢性潰瘍穿孔型（C群）に分け，臨床的背景を検討した．また，免疫組織化学染色により，潰瘍穿孔部周辺の *H. pylori* の有無，幽門腺領域の *H. pylori* 感染を定性的に評価し，病理形態学的所見との関連を検討した．C群は60例，A群は29例であった．臨床的背景では，潰瘍の既往，1週間以上の穿孔前症状，手術時の肉眼所見で両群に有意差を認めた．潰瘍穿孔部周辺に *H. pylori* は観察されず，幽門腺領域では81例に感染を認め，レベル1が20例，レベル2が35例，レベル3が26例であった．*H. pylori* 感染と病理形態学的所見の関連では，線維化や瘢痕形成，潰瘍周辺部の動脈壁の肥厚や線維化，好中球優位の炎症細胞浸潤，粘膜の炎症，浮腫，毛細管性出血について有意差が認められた．A群の55%がレベル1で，レベル2,3は28%であったが，C群は88%がレベル2,3であり，A群に比べ，有意に *H. pylori* の感染レベルが高かった．両群は臨床的背景だけでなく，*H. pylori* の感染レベルも有意に異なっていた．潰瘍形成から穿孔に至る機序は，急性型と慢性型で異なると推測され，特に急性潰瘍穿孔症例は，*H. pylori* 以外にも穿孔要因があることが示唆された．