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Helicobacter pylori Infection and Gastroduodenal Disease: a Comparison of Endoscopic Findings, Histology, and Urease Test Data

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ABSTRACT

To determine the prevalence and significance of *Helicobacter pylori* (*H. pylori*) infection, biopsies of the antral mucosa were obtained from 139 patients and 43 asymptomatic volunteers. The specimens were examined by hematoxylin-eosin staining and the urease test. The detection rate of *H. pylori* by histologic examination was 91.3% in patients with duodenal ulcer, 75.0% in those with combined duodenal and gastric ulcer, 63.6% in those with gastric ulcer, 22.9% in those with gastric carcinoma, 36.4% in those with gastric adenoma, 14.3% in those with gastric hyperplastic polyp, and 51.7% in those with gastritis, and the respective percentages detected by the urease test were 91.3%, 75.0%, 54.5%, 28.6%, 27.3%, 14.3%, and 44.8%. *H. pylori* was also detected in 10/43 (23.3%) asymptomatic healthy volunteers by histology and the urease test. The prevalence of *H. pylori* was significantly higher in the patients than in the asymptomatic healthy volunteers ($p<0.05$). *H. pylori* was detected in 62.9% of patients with endoscopic erosive gastritis and in 97.9% of those with histologically proven chronic active gastritis. The urease test was positive in 77/82 patients who were histologically positive for the organism (sensitivity: 93.9%), and it was negative in 98/100 patients who were negative by histology (specificity: 98.0%). Thus, there was over 90% agreement between the urease test and histology. Our investigations showed that *H. pylori* was closely related to peptic ulcers and antral gastritis, and that the urease test provides a simple, rapid and accurate diagnosis of *H. pylori* infection.

Key words: *Peptic ulcer, Gastritis, Gastric carcinoma, Helicobacter pylori infection*

Since *Campylobacter pylori* (now called *Helicobacter pylori*) was first isolated in 1983[35], this organism has been increasingly recognized as an important factor in the development of chronic gastritis and peptic ulcer disease. In addition, recent reports have indicated a close relationship between *Helicobacter pylori* (*H. pylori*) and gastric carcinoma[4,28]. The organisms have been observed in 55-86% of patients with gastritis[1,6,11,16,23,33], 57-96% of patients with gastric ulcer, and 70-100% of patients with duodenal ulcer[2,11,12,16,18,26,29-31,33]. Eradication of *H. pylori* results in a lower relapse rate of duodenal ulcer[8,19] as well as in the improvement of gastritis[5,10,27,31]. The fulfillment of Koch's postulates in human volunteer studies and investigations involving antimicrobial therapy[17,22] have shown that eradication of *H. pylori* coincides with the remission of gastritis, supporting the hypothesis that the organism is indeed the major cause of this condition.

Several diagnostic tests have been used to evaluate the presence of *H. pylori* in the gastric mucosa. Special culture techniques have been devised to grow this fastidious organism[18,30,34]. Histologic examination of gastric biopsy is performed after staining with hematoxylin-eosin[34], Giemsa stain[15], the Warthin-Starry technique[25] or acridine-orange[14]. More recently, an immunocytochemical technique utilizing an unlabeled anti-*H. pylori* antibody peroxidase-antiperoxidase method has been developed[24]. Rapid methods of identification utilizing the organism's urease activity have also been successful[9,32], including a ^{14}C-urea breath test[20,21]. *H. pylori* splits ^{14}C-urea into ammonia and $^{14}CO_2$. The $^{14}CO_2$ is absorbed and exhaled and can be measured. Serum IgM and IgG antibodies to *H. pylori* can be measured by complement fixation or by means of an enzyme-linked immunosorbent assay[3,7,21]. Each of these methods has its own advantages and disadvantages, with some being more widely available than others. In the present study, we confirmed that *H. pylori* infection is correlated

with gastritis and peptic ulcer disease, and also evaluated the usefulness of the rapid urease test for identifying this organism.

MATERIALS and METHODS

Patient population and study design: One hundred and thirty-nine patients who presented to the Gastroenterology Endoscopic Unit at Hiroshima University Medical Hospital between April 1990 and June 1991 for the endoscopic evaluation of upper GI symptoms or mass screening for gastric carcinoma were examined to detect the presence of *H. pylori*. The patient group consisted of 94 males and 45 females and their mean age (± SD) was 58.0 ± 16.2 years. At endoscopy, three biopsies were taken routinely from the midportion of the endoscopically normal antral mucosa, along the lesser curvature. One of these specimens was used for the rapid urease test (Delta West Ltd, Canning Vale, Australia), and the others were processed for histologic examination. New disinfected biopsy forceps were used to obtain each biopsy. A biopsy specimen of any lesion noted at endoscopy was also obtained for histologic evaluation.

In addition, antral mucosa biopsies obtained from 43 asymptomatic volunteers (40 males and 3 females with a mean age of 23.8 ± 5.5 years) were also subjected to the urease test and examined histologically. These subjects were either medical students or soldiers. Informed consent to the study was obtained from all patients and volunteers.

Urease test: All tests were evaluated by the same operator (S.O.). A test tablet containing 43.974 mg urea and 0.0075 mg phenol red was dissolved with 0.5 ml distilled water in one reaction vessel. A biopsy of the antrum was placed in this solution. A test was considered positive when the indicator turned from amber to dark pink, and most positive tests became so within 180 min. The test was considered as negative if there was no color change, or only a partial color change to orange, at the end of 24 h.

Histological examination: Two or more specimens obtained from the gastric antral mucosa were placed in 10% formalin and subsequently stained with hematoxylin and eosin. All specimens were then evaluated by one investigator (K.H.) under a × 100 oil immersion lens. This investigator had no knowledge of patient identity and of the results of the urease test. If the characteristic spiral *H. pylori* organisms were seen, the result was considered positive. If *H. pylori* was not evident in the specimens, the original tissue blocks were recut, stained with Giemsa stain, and re-examined. In addition, two specimens from the endoscopically normal antral mucosa were classified for gastritis as follows: normal, no inflammatory cells or a normal number of such cells; chronic inactive gastritis, an increased number of lymphocytes and plasma cells in the lamina propria; chronic active gastritis, neutrophil infiltration in addition to the changes of chronic gastritis; and atrophic gastritis, complete or near complete loss of pyloric glands, and/or presence of intestinal metaplasia. Chronic inactive gastritis was subclassified as mild or severe and the presence of intestinal metaplasia was noted. The number of bacteria present was graded as follows: Nil = no bacteria seen. Mild = occasional bacteria present, but not seen in every high power field. Moderate = bacterial numbers intermediate between mild and severe. Severe = numerous bacteria in all fields, usually confluent and covering the entire mucosal surface.

Endoscopic features of antral gastritis: The endoscopic features of antral gastritis were categorized as follows: (1) normal; (2) erosive gastritis, defined as the presence of gastric erosions; (3) superficial gastritis, defined as the presence of erythema without gastric erosions; and (4) atrophic gastritis, defined as an easily visible venous plexus or the presence of intestinal metaplasia.

Statistical analysis: The Fisher exact test or the chi-squared test was used to determine the significance of differences between the groups.

RESULTS

Patients were considered positive for *H. pylori* if the bacteria were detected by hematoxylin-eosin and/or Giemsa staining (Fig. 1). The associations between the various endoscopic diagnoses and the presence of *H. pylori* are summarized in Table 1. The organism was found by histologic examination in 21/23 (91.3%) patients with duodenal ulcer, 9/12 (75.0%) patients with combined duodenal and gastric ulcers, 14/22 (63.6%) patients with gastric ulcer, 8/35 (22.9%) patients with gastric carcinoma, 4/11 (36.3%) patients with gastric adenoma, 1/7 (14.3%) patients with gastric polyp, and 15/29 (51.7%) patients with gastritis. The percentages of these groups who were positive to the urease test were 91.3%, 75.0%, 54.5%, 28.6%, 27.3%, 14.3%, and 44.8% respectively. *H. pylori* was detected by histology and the urease test in 10/43 (23.3%) healthy volunteers. When endoscopic examination was performed for this protocol, one healthy volunteer (a 23-year-old male) had an unsuspected active duodenal ulcer, 10/43 volunteers had mild erosive gastritis, and the rest were normal.

The relationship between an endoscopic diagnosis of antral gastritis and the presence of *H. pylori* is shown in Table 2. Of the total of 182 subjects undergoing endoscopy (139 patients and 43 volunteers), 32 were diagnosed as having normal mucosa, 10 as having superficial gastritis, 70 as having erosive gastritis, and 70 as having atrophic gastritis. *H. pylori* was detected by histology in 13/32 (40.6%) patients with an endoscopically normal antral mucosa, in 44/70 (62.9%) patients with erosive gastritis, and in 25/70 (35.7%) patients with atrophic gastritis. On the other hand, *H. pylori* could not

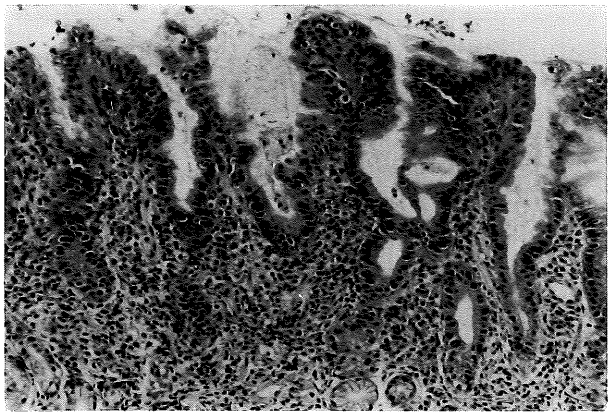

Fig. 1 a. The characteristic appearance of *H. pylori* infection in gastric biopsy taken from the antrum. This is a severe active gastritis with widespread neutrophilic inflammation and marked choronic inflammation. Neutrophils are present within the gastric epithelium. Epithelial degeneration and mucin depletion are also seen. (Hematoxylin and eosin, original magnification × 66)

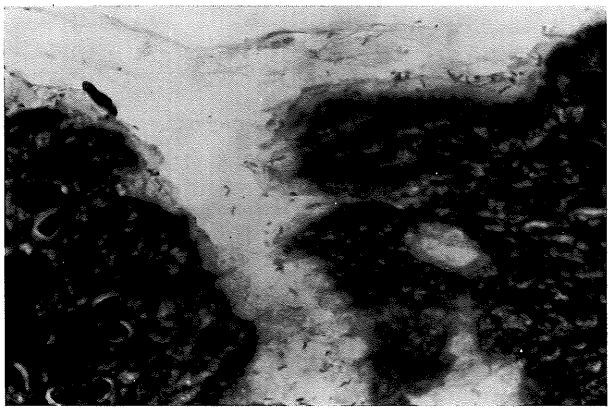

Fig. 1 b. *H. pylori* as visualized with the Giemsa stain. The bacteria appear as dark spirals lining the epithelial cells and within the mucus layer. (Original magnification × 330)

be detected in 10 patients with superficial gastritis. The detection rates of the organism by the urease test were 40.6% (normal), 61.4% (erosive), and 32.9% (atrophic). The relationship between the histological diagnosis of the antral mucosa and *H. pylori* is shown in Table 3. In all 20 patients with histologically proven normal mucosa, *H. pylori* could not be detected by histologic examination or the urease test. *H. pylori* was detected by histology in 10/51 (19.6%) patients with mild inactive gastritis, in 13/25 (52.0%) patients with moderate inactive gastritis, in 9/16 (56.3%) patients with severe inactive gastritis, in 47/48 (97.9%) patients with active gastritis, and in 3/22 (13.6%) patients with atrophic gastritis.

A urease test was performed in all 139 patients and all 43 healthy volunteers, and the results were compared with those of histologic examination (Table 4). There was a very close relationship between the detection of *H. pylori* by histology and by a positive rapid urease test. The urease test detected *H. pylori* in 77/82 patients with histologic evidence of the organism (sensitivity: 93.9%), and the test was negative in 98/100 patients who were negative by histologic examination (specificity: 98.0%). The relationship between the histologic grade of *H. pylori* infection and the urease reaction time is shown in Table 5. Of the 82 specimens in which *H. pylori* was detected, 77 had a corresponding positive urease test. The greater the number of *H. pylori* seen in the biopsy specimen, the more rapidly the end-point color developed in the test wells. Among 82 specimens where *H. pylori* was detected by histology, 63 (76.8%) were positive by the urease test within 180 min.

DISCUSSION

The present study confirms previous reports that the high prevalence of *H. pylori* infection is closely related to chronic gastritis and peptic ulcer disease. In addition, we showed that the urease test provides a rapid and accurate method for the diagnosis of *H. pylori* infection. The prevalence of *H. pylori* in gastric ulcer patients is reported as 70% or more and it is 80-100% in those with duodenal ulcer[2,11,12,16,18,26,29-31,33]. Our study found a prevalence of *H. pylori* in gastric ulcer patients that was similar to the reported level. Duodenal ulcer patients also had a similar prevalence of *H. pylori*, but the prevalence rate of 22.9% in gastric carcinoma was lower than that reported by Parsonnet[28].

The asymptomatic young volunteers had a low incidence (23.3%) of *H. pylori* infection of the antral mucosa, which was similar to the 13%-32% incidence of *H. pylori* in healthy volunteers reported by others[6,29,31]. It is of interest that one of the *H. pylori*-positive asymptomatic volunteers had an unsuspected active duodenal ulcer.

Our investigation also confirmed that the prevalence of *H. pylori* infection was closely related to a diagnosis of antral gastritis by endoscopy or histology. The infection rate in patients with endoscopic erosive gastritis was 62.9%, and this was significantly higher than that in patients with endoscopically normal antral mucosa (40.6%), superficial gastritis (0%) or atrophic gastritis (35.7%). The organism was identified histologically in 97.9% of the patients with chronic active gastritis and in 34.8% of those with inactive gastritis. On the other hand, *H. pylori* could not be detected in 20 patients with a histologically normal antrum, and the incidence was a low 13.6% in patients with atrophic gastritis. The reasons why *H. pylori* was detected in some patients with normal endoscopic findings and was not detected in those with severe gastritis remain largely obscure.

The sensitivity and specificity of the urease test was very good, and this indicates that it provides

Table 1. Endoscopic diagnosis and the presence of *H. pylori***

Endoscopic diagnosis	No. of patients	Mean age (yr)	Detection of *H. pylori*	
			Histology n (%)	Urease test n (%)
Duodenal ulcer	23	42.4	21 (91.3)*	21 (91.3)*
Combined duodenal and gastric ulcer	12	57.3	9 (75.0)*	9 (75.0)*
Gastric ulcer	22	60.0	14 (63.6)*	12 (54.5)*
Gastric carcinoma	35	68.2	8 (22.9)	10 (28.6)
Gastric adenoma	11	68.7	4 (36.4)	3 (27.3)
Gastric polyp	7	61.7	1 (14.3)	1 (14.3)
Gastritis	29	51.8	15 (51.7)*	13 (44.8)*
Healthy volunteers	43	23.8	10 (23.3)	10 (23.3)

* $p<0.05$: compared with the asymptomatic healthy volunteers.
** The presence of *H. pylori* was detected in the endoscopically normal antral mucosa.

Table 2. Endoscopic findings in relation to detection of *H. pylori***

Endoscopic appearance of antral mucosa	No. of patients	Detection of *H. pylori*	
		Histology n (%)	Urease test n (%)
Normal mucosa	32	13 (40.6)	13 (40.6)
Superficial gastritis	10	0 (0)*	0 (0)*
Erosive gastritis	70	44 (62.9)*	43 (61.4)*
Atrophic gastritis	70	25 (35.7)	23 (32.9)

* $p<0.05$: compared with nomal mucosa.
** The presence of *H. pylori* was detected in the endoscopically normal antral mucosa.

Table 3. Histology of the endoscopically normal antral mucosa in relation to the presence of *H. pylori*

Mucosal histology	No. of patients	Detection of *H. pylori*	
		Histology n (%)	Urease test n (%)
Normal mucosa	20	0 (0)	0 (0)
Chronic inactive gastritis			
mild	51	10 (19.6)*	8 (15.7)*
moderate	25	13 (52.0)*	13 (52.0)*
severe	16	9 (56.3)*	11 (68.8)*
Active chronic gastritis	48	47 (97.9)*	44 (91.7)*
Atrophic gastritis	22	3 (13.6)*	3 (13.6)*

* $p<0.05$: compared with normal mucosa.

Table 4. Comparison of detection of *H. pylori* by histologic examination and the urease test

Histologic examination	No. of patients	Urease test	
		Negative n (%)	Positive n (%)
Negative	100	98 (98.0)	2 (2.0)
Positive	82	5 (6.1)	77 (93.9)

Table 5. Comparison of histologic grade of *H. pylori* infection and the urease test reaction time

H. pylori infection grade	No. of specimens	Urease reaction time (min)			
		0-30	>30-180	>180	Negative
Nil	100	0	0	2	98
Mild	42	10	14	13	5
Moderate	22	10	11	1	0
Severe	18	15	3	0	0

a useful method for the diagnosis of *H. pylori* infection. Culture of this organism is quite difficult and requires a motivated microbiologist to achieve success. Special handling of specimens is also required (prompt incubation and processing), it takes 2-5 days to obtain a result, and the sensitivity is low. A major advantage of detecting *H. pylori* by histological examination using hematoxylin-eosin staining[34] or Giemsa staining[15] is that an opportunity is provided to evaluate the biopsied mucosal tissue for microscopic gastritis. This is especially important in view of studies that suggest that the presence of *H. pylori* is closely related to the pathogenesis of peptic ulcer disease or antral gastritis. However, one disadvantage is that reliable interpretation of the stained specimens requires some practice. The rapid urease test, on the other hand, requires no special skill to interpret and can usually be completed within 180 min so that a diagnosis can be made before the patient leaves hospital. Schnell et al. reported that the greater is the number of organisms in the biopsy specimen, the more rapidly the indicator turns positive[32].

The role of *H. pylori* in gastric carcinogenesis has become a topic of current interest, since *H. pylori* infection is associated with chronic gastritis and chronic atrophic gastritis is associated with gastric carcinoma. Recent studies have indicated a close relationship between *H. pylori* infection and gastric carcinoma[4,28] or atrophic gastritis of the fundus[13]. However, we found histologic evidence of *H. pylori* in the antrum of only 22.9% of our patients with gastric carcinoma in contrast to other reports of a high incidence of this organism in gastric carcinoma patients. Parsonnet et al. detected *H. pylori* histologically in 33/37 (89.2%) intestinal-type gastric carcinoma patients, and in 7/22 (31.8%) with diffuse-type gastric carcinoma[28]. A more recent report has demonstrated that patients with atrophic gastritis of the fundus have a high prevalence of *H. pylori* seropositivity and a lower prevalence of *H. pylori* in histological specimens[13]. It is well known that intestinal-type gastric carcinoma develops in association with atrophic gastritis. Therefore, *H. pylori* infection might be related to the pathogenesis of intestinal-type gastric carcinoma, because this organism may induce atrophic gastritis affecting the gastric body.

In conclusion, our results indicate that *H. pylori* infection might play a role in the development of peptic ulcer disease and antral gastritis. The urease test provides an easy, accurate and inexpensive method for the identification of this organism on a routine basis. However, a link between *H. pylori* and gastric carcinoma or atrophic gastritis could not be confirmed in this study, and further investigations, including serological or prospective studies, are needed to clarify this issue.

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