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World J Gastroenterol 2005;11(6):791-796
World Journal of Gastroenterology ISSN 1007-9327

• *BASIC RESEARCH* •

Helicobacter pylori infection, glandular atrophy and intestinal metaplasia in superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer and early gastric cancer

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Received: 2004-04-22 Accepted: 2004-07-15

Abstract

AIM: To evaluate the histological features of gastric mucosa, including *Helicobacter pylori* infection in patients with early gastric cancer and endoscopically found superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer.

METHODS: The biopsy specimens were taken from the antrum, corpus and upper angulus of all the patients. Giemsa staining, improved toluidine-blue staining, and *H pylori*-specific antibody immune staining were performed as appropriate for the histological diagnosis of *H pylori* infection. Hematoxylin-eosin staining was used for the histological diagnosis of gastric mucosa inflammation, gastric glandular atrophy and intestinal metaplasia and scored into four grades according to the Updated Sydney System.

RESULTS: The overall prevalence of *H pylori* infection in superficial gastritis was 28.7%, in erosive gastritis 57.7%, in gastric erosion 63.3%, in gastric ulcer 80.8%, in early gastric cancer 52.4%. There was significant difference ($P<0.05$), except for the difference between early gastric cancer and erosive gastritis. *H pylori* infection rate in antrum, corpus, angulus of patients with superficial gastritis was 25.9%, 26.2%, 25.2%, respectively; in patients with erosive gastritis 46.9%, 53.5%, 49.0%, respectively; in patients with gastric erosion 52.4%, 61.5%, 52.4%, respectively; in patients with gastric ulcer 52.4%, 61.5%, 52.4%, respectively; in patients with early gastric cancer 35.0%, 50.7%, 34.6%, respectively. No significant difference was found among the different site biopsies in superficial gastritis, but in the other diseases the detected rates were higher in corpus biopsy ($P<0.05$). The grades of mononuclear cell infiltration and polymorphonuclear cell infiltration, in early gastric cancer patients, were significantly higher than that in superficial gastritis patients, lower than that in gastric erosion and gastric ulcer patients ($P<0.01$); however, there was no significant difference compared with erosive gastritis. The grades of mucosa glandular atrophy and intestinal metaplasia were significantly highest in early gastric cancer, lower in gastric ulcer, the next were erosive gastritis, gastric erosion, the lowest in superficial gastritis ($P<0.01$). Furthermore, 53.3% and 51.4% showed glandular atrophy and intestinal metaplasia in angular biopsy specimens, respectively; but only 40.3% and 39.9% were identified in antral biopsy, and 14.1% and 13.6% in corpus biopsy; therefore, the angulus was more reliable for the diagnosis of glandular atrophy and intestinal metaplasia compared with antrum and corpus ($P<0.01$). The positivity rate of glandular atrophy and intestinal metaplasia of superficial gastritis with *H pylori*-positivity was 50.7%, 34.1%; of erosive gastritis 76.1%, 63.0%; of gastric erosion 84.8%, 87.8%; of gastric ulcer 80.6%, 90.9%; and of early gastric cancer 85.5%, 85.3%, respectively. The positivity rate of glandular atrophy and intestinal metaplasia of superficial gastritis with *H pylori*-negativity was 9.9%, 6.9%; of erosive gastritis 42.5%, 42.1%; of gastric erosion 51.1%, 61.9%; of gastric ulcer 29.8%, 25.5%; and of early gastric cancer 84.0%, 86.0%, respectively. The positivity rate of glandular atrophy and intestinal metaplasia of superficial gastritis, erosive gastritis, gastric erosion, and gastric ulcer patients with *H pylori* positivity was significantly higher than those with *H pylori* negativity ($P<0.01$); however, there was no significant difference in patients with early gastric cancer with or without *H pylori* infection.

CONCLUSION: The progression of the gastric pre-cancerous lesions, glandular atrophy and intestinal metaplasia in superficial gastritis, gastric erosion, erosive gastritis and gastric ulcer was strongly related to *H pylori* infection. In depth studies are needed to evaluate whether eradication of *H pylori* infection will really diminish the risk of gastric cancer.

Key words: *Helicobacter pylori*; Glandular atrophy; Intestinal metaplasia; Early gastric cancer

Zhang C, Yamada N, Wu YL, Wen M, Matsuhisa T, Matsukura N. *Helicobacter pylori* infection, glandular atrophy and

intestinal metaplasia in superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer and early gastric cancer. *World J Gastroenterol* 2005; 11(6): 791-796
http://www.wjgnet.com/1007-9327/11/791.asp

INTRODUCTION

The discovery of *Helicobacter pylori* (*H pylori*) offered the etiologic agent of the initiating event of the inflammatory cascade[1,2]. It has been confirmed that the development of gastric cancer spans over several decades sequentially starting with the acquisition of *H pylori* infection and the development of chronic active gastritis[3,4]. Over time, the development of glandular atrophy and intestinal metaplasia takes place in a subset of patients. Finally, gastric cancer would eventually arise[5]. It was suggested that *H pylori* infection leads to an increased risk, in the order of 4 to 9 folds, of developing precancerous gastric conditions especially when the infection occurs in childhood[6-9]. In 1994 the International Agency for Research on Cancer (IARC) monograph committee classified *H pylori* as a class I carcinogen to humans[10]. On the other hand, *H pylori* are also the cause of other gastric diseases, such as peptic ulcer, gastric mucosa-associated lymphoma[13-17]. Previous histological studies have reported the association between *H pylori* infection and gastric cancer mainly using gastrectomy specimens from patients with advanced gastric cancer. However, the results were not always consistent; higher rates of serologically and histologically detected *H pylori* positivity have been reported for early stage cancer than for advanced cancer[11,12]. Therefore, to evaluate the significance of *H pylori* infection in gastric carcinogenesis, samples obtained from patients with an early stage cancer could be more informative than those from patients with advanced-stage cancer. Additionally, because both the incidence of gastric cancer and the frequency of *H pylori* infection are much higher in Japanese than in most Western populations, it would be of particular interest to examine the association between endoscopically found superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer and early gastric cancer in Japanese patients with *H pylori* infection. Further, it is more accurate to compare the presence of *H pylori* infection, glandular atrophy and intestinal metaplasia in age- and gender-matched subjects[18].

MATERIALS AND METHODS

Patients

All patients were prospectively selected from subjects who underwent upper gastrointestinal endoscopy screening with present or past abdominal complaints at Nippon Medical School hospitals from November 1994 to November 2003. To perform a case-controlled study, five age (±2 years) and sex-matched control subjects for each cancer patient was randomly selected from the same series of subjects with superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer or early gastric cancer. Subjects were considered to be eligible for inclusion into the present study when their endoscopic diagnosis was superficial gastritis, gastric erosion, erosive gastritis or gastric ulcer. Early gastric cancer was pathologically diagnosed, as defined by the Japanese Gastroenterological Society, by the growth of malignant tumor confined to the mucosa and submucosa of the stomach regardless of the presence or absence of metastatic disease in the perigastric lymph nodes. Patients were excluded from the study if they had received anti-ulcer agents or antibiotics during the 2 mo before endoscopy or had previous histories of duodenal ulcers, or gastric surgery. The study comprised 286 patients with early gastric cancer aged from 38 to 90 years (mean age 65.7±10.8), which included 220 males and 66 females; 286 patients with superficial gastritis aged from 38 to 88 years (mean age 65.3±9.9); 286 patients with gastric erosion aged from 38 to 90 years (mean age 65.3±10.4); 286 patients with erosive gastritis aged from 38 to 90 years (mean age 65.3±10.4); 286 patients with gastric ulcer aged from 38 to 92 years (mean age 65.7±10.8). All patients gave informed consent before their endoscopies and the study was approved by the Ethics Committee of Nippon Medical School.

Histological analysis

Biopsy specimens for histological diagnosis were obtained endoscopically from the greater curvature of the lower, the upper corpus and the lesser curvature of the lower corpus of the stomach, according to the triple-site gastric biopsy method, in all cases. Biopsy specimens were fixed overnight in buffered formalin, embedded in paraffin, cut to 3-μm thickness, and stained with hematoxylin-eosin staining, improved toluidine-blue staining, Giemsa staining and *H pylori*-specific antibody immune staining (Dako, Denmark). Identification of *H pylori* was performed using the improved toluidine-blue staining, Giemsa staining and *H pylori*-specific antibody immune staining. In accordance with the Updated Sydney System, the degree of gastric mucosal inflammation (mononuclear cell infiltration), polymorphonuclear cell infiltration, glandular atrophy, and intestinal metaplasia were classified into four grades as follows: 0 = none, 1 = mild, 2 = moderate and 3 = severe. Histologically, *H pylori* infection was considered negative if *H pylori* were absent from all biopsy sites stained with improved toluidine-blue staining, Giemsa staining and *H pylori*-specific antibody immune staining. *H pylori* infection was considered positive if at least one of the histology tests was positive[19,20].

Statistical analysis

The prevalence of *H pylori* infection, rates of gastric mucosal inflammation, polymorphonuclear cell infiltration, glandular atrophy and intestinal metaplasia were compared using the χ^2 test for 4-fold table. The difference in grades of mononuclear cell infiltration, polymorphonuclear cell infiltration, glandular atrophy, and intestinal metaplasia between diseases was compared by Mann-Whitney *U*-test. *P* values <0.05 were considered statistically significant.

RESULTS

Prevalence of H pylori

The positivity rates for *H pylori* infection in studied patients are shown in Table 1. The overall prevalence of *H pylori*

infection in superficial gastritis was 28.7%, erosive gastritis 57.7%, gastric erosion 63.3%, gastric ulcer 80.8%, and early gastric cancer 52.4%. The prevalence of *H pylori* infection in early gastric cancer was significantly higher than that of superficial gastritis, lower than that of gastric erosion, gastric ulcer (all $P<0.05$); however, there was no significant difference in the prevalence of *H pylori* infection between early gastric cancer and erosive gastritis. The prevalence was also higher in gastric ulcer and gastric erosion than in superficial gastritis and erosive gastritis (all $P<0.05$). No significant difference was found in the *H pylori* infection rates among the different biopsy sites in superficial gastritis, but in the other diseases the rates were higher in corpus biopsy.

Table 1 ***H pylori*** **infection identified in different biopsy sites in associated diseases**

Endoscopical diagnosis	Cases	*H pylori* infective rate (%)			
		Antrum	Corpus	Angle	Overall
Superficial gastritis	286	25.9	26.2	25.2	28.7
Erosive gastritis	286	46.9	53.5	49.0	57.7
Gastric erosion	286	52.4	61.5	52.4	63.3
Gastric ulcer	286	65.0	78.0	61.2	80.8
Early gastric cancer	286	35.0	50.7	34.6	52.4

Grades of mononuclear cell infiltration, polymorphonuclear cell infiltration, mucosal glandular atrophy and intestinal metaplasia

The grades of mononuclear cell infiltration and polymorphonuclear cell infiltration, mucosal glandular atrophy and intestinal metaplasia in patients are shown in Table 2. The grades of mononuclear cell infiltration and polymorphonuclear cell infiltration in early gastric cancer patients were significantly higher than that in superficial gastritis patients and lower than that in gastric erosion and gastric ulcer patients (all $P<0.01$); however, there was no significant difference compared with erosive gastritis. The grades of mononuclear cell infiltration and polymorphonuclear cell infiltration in gastric ulcer, gastric erosion, and erosive gastritis patients were also significantly higher than that in superficial gastritis patients (all $P<0.01$). On the other hand, they were significantly lower than that in gastric ulcer patients; (both $P<0.01$).

The grades of mucosal glandular atrophy and intestinal metaplasia were significantly higher in early gastric cancer, lower in gastric ulcer, erosive gastritis, and gastric erosion and the lowest in superficial gastritis (all $P<0.01$). Furthermore, 53.3% and 51.4% showed glandular atrophy and intestinal metaplasia in angular biopsy specimens, respectively; however, only 40.3% and 39.9% were identified in antral biopsy, 14.1% and 13.6% in corpus biopsy. Therefore, the angulus was more reliable for the diagnosis of glandular atrophy and intestinal metaplasia compared to antrum and corpus (both $P<0.01$).

Rates of inflammation, activity, mucosal glandular atrophy and intestinal metaplasia in patients with and without H pylori infection

Rates of mononuclear cell infiltration, polymorphonuclear cell infiltration, glandular atrophy and intestinal metaplasia in patients with and without *H pylori* are shown in Table 3.

The positivity rate of chronic inflammation of superficial gastritis, erosive gastritis, gastric erosion, and gastric ulcer patients with *H pylori*-positivity was significantly higher than those with *H pylori*-negativity (all $P<0.01$); however, there was no significant difference in patients with early gastric cancer with or without *H pylori* infection.

Mononuclear cell infiltration rate was significantly higher in superficial gastritis, erosive gastritis and gastric erosion, gastric ulcer or early gastric cancer patients with *H pylori*-positivity than *H pylori*-negative patients (all $P<0.01$).

Table 2 **The grade of mononuclear cell infiltration, polymorphonuclear cell infiltration, glandular atrophy and intestinal metaplasia in studied patients (%)**

Diagnosis	Mononuclear cell infiltration				Polymorphonuclear cell infiltration				Glandular atrophy				Intestinal metaplasia			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Superficial gastritis	40.9	34.3	10.1	14.7	72.7	3.5	4.5	19.2	78.7	17.6	2.2	1.5	85.3	4.9	4.2	5.6
Erosive gastritis	11.2	32.9	19.2	36.7	40.2	6.6	12.9	40.2	38.8	30.6	17.3	13.3	45.8	16.4	14.7	23.1
Gastric erosion	3.8	29.0	21.0	46.2	33.9	3.8	10.1	52.1	28.3	23.2	24.5	24.1	21.7	18.5	23.4	36.4
Gastric ulcer	4.2	14.3	14.0	67.5	17.8	3.1	7.7	71.3	29.2	17.7	21.8	31.3	21.7	2.4	2.4	73.4
Early gastric cancer	0.7	42.3	29.4	27.6	40.2	10.1	1.9	37.8	20.3	20.7	18.1	40.9	14.3	12.2	18.9	54.5

Table 3 **Rates of inflammation, activity, glandular atrophy and intestinal metaplasia in patients with and without *H pylori* infection (%)**

Diagnosis	Mononuclear cell infiltration *H pylori*		Polymorphonuclear cell infiltration *H pylori*		Glandular atrophy *H pylori*		Intestinal metaplasia *H pylori*	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Superficial gastritis	93.9[b]	45.1	90.2[b]	2.0	50.7[b]	9.9	34.1[b]	6.9
Erosive gastritis	98.8[b]	75.2	97.0[b]	9.1	76.1[b]	42.5	63.0[b]	42.1
Gastric erosion	100.0[b]	89.5	99.4[b]	8.6	84.8[b]	51.1	87.8[b]	61.9
Gastric ulcer	99.1[b]	81.8	99.1[b]	10.9	80.6[b]	29.8	90.9[b]	25.5
Early gastric cancer	100.0	98.5	100.0[b]	15.4	85.5	84.0	85.3	86.0

[b]$P<0.01$ *vs H pylori*-negative group.

The positivity rate of mucosa glandular atrophy and intestinal metaplasia of superficial gastritis, erosive gastritis, gastric erosion, and gastric ulcer patients with *H pylori*-positivity was significantly higher than those with *H pylori*-negativity (all $P<0.01$); however, there was no significant difference in patients with early gastric cancer with or without *H pylori* infection ($P<0.01$).

DISCUSSION

Since the discovery of *H pylori*, many studies have implicated infection with this bacterium in the pathogenesis of gastric cancer. But prevalence of *H pylori* varies widely between and within populations. Risk factors for *H pylori* infection have been extensively studied. The prevalence of *H pylori* infection among males appears to be higher than that among females. It is also associated with age, lifestyle, ethnic, and economic factors. In order to decrease the effect of these risk factors on the study results as much as possible, we performed a case-controlled study. Five age- and gender-matched control subjects for each early gastric cancer patient was randomly selected from the same series of subjects with superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer[21-25,31].

Our age- and gender-matched results suggest that from superficial gastritis, erosive gastritis, gastric erosion to gastric ulcer, as *H pylori* infection rates increased, the pre-malignant lesions of glandular atrophy and intestinal metaplasia also increased gradually. But in early gastric cancer patients the *H pylori* infection rate was not very high; the reason might be in early gastric cancer both mucosa atrophy and intestinal metaplasia were very serious, which was unfavorable for *H pylori* growth; therefore *H pylori* decreased gradually. As to the distribution of *H pylori* and inflammation in the stomach, Genta reported that *H pylori* were distributed evenly throughout the stomach[26]. In the present study, we found that the prevalence of *H pylori* infection was not significantly different among the different biopsy sites in superficial gastritis, but in the other diseases the detected rates were higher in corpus biopsy. This finding was a little different from Genta's observation. In comparison between *H pylori*-positive and *H pylori*-negative patients, mononuclear cell infiltration was more severe in *H pylori*-positive patients with superficial gastritis, erosive gastritis, gastric erosion, gastric ulcer or early gastric cancer than *H pylori*-negative patients, and it was related between the grade of mononuclear cell infiltration, polymorphonuclear cell infiltration and the grade of *H pylori* infection. More intense bacterial infection and more severe polymorphonuclear cell infiltration may contribute more to DNA damage and promote carcinogenesis in patients with gastric cancer. Furthermore, chronic *H pylori* infection is also associated with increased gastric cell turnover, probably of importance in malignant transformation[27,28].

The finding of a high incidence of chronic gastritis in patients with gastric cancer and gastric ulcer supports previous studies. All of the gastric cancer and gastric ulcer were found in the setting of atrophic gastritis. Similarly, Sipponen has reported a study of 54 patients with gastric cancer, among whom 38 (70%) had *H pylori* infection. Only five patients (16%) had normal mucosa, but had no evidence of *H pylori* infection by serology or histology[29]. Craanen showed that atrophic mucosal changes were present in 90.3% of patients with intestinal-type early gastric cancer. *H pylori* infection was found in 63.6% of patients with intestinal-type early gastric cancer and in 54.5% of patients with diffuse-type early gastric cancer[30]. In Western countries, the prevalence of *H pylori* infection is 70-80% in gastric cancer patients, but 10-20% of gastric cancer patients develop in an apparently *H pylori*-negative stomach. It is well known that the prevalence of *H pylori* infection and gastric cancer is higher in Japan than in Western countries. In our study, of 286 patients with early gastric cancer 150 patients had positive *H pylori* infection, 136 had negative *H pylori* infection, but most of them had moderate to severe atrophic gastritis, the atrophic rate was 85.5% and 84.0% respectively. The prevalence of *H pylori* infection and early gastric cancer in this study was 52.4%, also similar to the findings reported by Craanen[30].

Glandular atrophy and intestinal metaplasia were found in more than half of *H pylori*-positive patients but were remarkably low in the *H pylori*-negative patients. These results confirm the tight link between *H pylori* infection, atrophic gastritis and intestinal metaplasis in the stomachs of Japanese. In early gastric cancer patients, both glandular atrophy and intestinal metaplasia were found to be higher; however, there was no significant difference between *H pylori*-positive and negative patients. Occasionally, it was found in glandular atrophy and intestinal metaplasia tissues *H pylori* negative, while in the tissues without glandular atrophy or intestinal metaplasia it might be found *H pylori* positive. These findings suggest that most patients with intestinal metaplasia and glandular atrophy have been infected with *H pylori* at some stage. *H pylori* infection may provide the proper environment for atrophic gastritis and intestinal metaplasia to occur. At the final stage of the disease, gastric atrophy with intestinal metaplasia is not a hospitable environment for *H pylori* and is associated with a dramatic reduction or even disappearance of the organism[31-35]. Furthermore, we found glandular atrophy and intestinal metaplasia were more frequent and severe in angulus and antrum, where gastric cancer occurs more frequently than in the corpus. In comparison with *H pylori* infection, the presence of intestinal metaplasia in the lesser curvature of the angulus was an increased risk for the development of gastric cancer.

In intestinal metaplasia in all patients with *H pylori* positivity, it was found that from superficial gastritis, erosive gastritis, gastric erosion to gastric ulcer, and early gastric cancer, both glandular atrophy and intestinal metaplasia significantly increased. This result is in accordance with the epidemiologic and pathologic studies of Correa, which revealed the temporal association of chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, epithelial dysplasia, and finally gastric cancer evolution[36].

There is increasing evidence that *H pylori* strains are highly diverse genomically. Several *H pylori* virulence-associated genes have been found in Western populations to be associated with an increased risk of gastric cancer and pre-cancerous lesions[37]. Studies from Japan have confirmed that IL-1β polymorphisms do contribute to the gastric acid secretory response to *H pylori* infection and

subsequently to clinical sequelae[38,39]. These outcomes range from, at one end of the spectrum, hypochlorhydria and atrophic gastritis with an increased risk of cancer, and on the other hand, high acid secretion and duodenal ulcer disease. In an important extension to this work, Figueriedo genotyped a large population with chronic gastritis and gastric cancer for polymorphisms of the genes for both IL-1β and its receptor, and for the *vac*A and *cag*A genotypes of the infecting *H pylori* strain[40]. Combinatorial analysis of both bacterial and host genotypes demonstrated an enormous difference in the risk of gastric cancer, depending on particular mixtures of *H pylori* virulence and host genetic factors, thus demonstrating the importance of considering both *H pylori* and host genetics in gastric cancer risk assessment. Infection with the *vac*A s1a/m1 strain has also been shown to be associated with greater mucosa neutrophil and lymphocyte infiltration. However, previous studies have shown that most *H pylori* strains in Japan are *cag*A positive and of the *vac*A s1a/m1 genotype[41-43]. Therefore, our results suggest that variabilities in host response to *H pylori* infection play an important role in the occurrence of intense gastritis, glandular atrophy and intestinal metaplasia in patients with superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer or early gastric cancer. However, because we used forceps biopsies, there was also the possibility of sampling error in the case of focal atrophy or intestinal metaplasia.

On the other hand, in the present study, infection of *H pylori*, glandular atrophy and intestinal metaplasia of gastric erosion were more serious than that of erosive gastritis by pathological diagnosis. These were not in accordance with our endoscopic findings in which erosive gastritis was more serious than gastric erosion. The possible reasons need to be evaluated further in the future.

In conclusion, the progression of gastric precancerous lesions, glandular atrophy and intestinal metaplasia in superficial gastritis, gastric erosion, erosive gastritis and gastric ulcer is strongly related to *H pylori* infection. Prospective studies are needed to evaluate whether eradication of *H pylori* infection will really diminish the risk of gastric cancer.

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Edited by Zhu LH