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Duodenal gastric metaplasia and *Helicobacter pylori* infection in patients with diffuse nodular duodenitis

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Abstract

Whether the regression of gastric metaplasia in the duodenum can be achieved after eradication of *Helicobacter pylori* is not clear. The aim of the present study was to investigate the relationship between *H. pylori* infection and gastric metaplasia in patients with endoscopic diffuse nodular duodenitis. Eighty-six patients with endoscopically confirmed nodular duodenitis and 40 control patients with normal duodenal appearance were investigated. The *H. pylori*-positive patients with duodenitis received anti-*H. pylori* triple therapy (20 mg omeprazole plus 250 mg clarithromycin and 400 mg metronidazole, all twice daily) for one week. A control endoscopy was performed 6 months after *H. pylori* treatment. The *H. pylori*-negative patients with duodenitis received 20 mg omeprazole once daily for 6 months and a control endoscopy was performed 2 weeks after treatment. The prevalence of *H. pylori* infection was 58.1%, and the prevalence of gastric metaplasia was 57.0%. Seventy-six patients underwent endoscopy again. No influence on the endoscopic appearance of nodular duodenitis was found after eradication of *H. pylori* or acid suppression therapy. However, gastric metaplasia significantly decreased and complete regression was achieved in 15/28 patients (53.6%) 6 months after eradication of *H. pylori*, accompanied by significant improvement of other histological alterations. Only mild chronic inflammation, but not gastric metaplasia, was found in the control group, none with *H. pylori* infection in the duodenal bulb. Therefore, *H. pylori* infection is related to the extent of gastric metaplasia in the duodenum, but not to the presence of diffuse nodular duodenitis.

Key words
• Nodular duodenitis
• *Helicobacter pylori*
• Gastric metaplasia

Introduction

Helicobacter pylori infection is a major cause of many gastroduodenal diseases, especially chronic gastritis, duodenal ulcer, and duodenitis. Since the colonization of the duodenum by *H. pylori* occurs only in regions of gastric metaplasia (GM), the development of duodenal GM is critically important in the pathogenesis of duodenal ulcer

and duodenitis. In previous studies, the prevalence of GM was 72 to 90% in patients with duodenal ulcer, 40 to 95% in patients with duodenitis, and 0 to 33% in patients with normal endoscopic duodenal appearance (1,2).

GM is generally believed to occur as a non-specific response to acid/peptic damage. It has been speculated that *H. pylori* infection induces a high level of acid burden in the duodenum by increasing gastrin secretion, which may influence the development of GM. It has been shown that the amount of *H. pylori* in the duodenal bulb may be related to the extent of GM (3). Theoretically, regression of GM may be induced by eradication of *H. pylori* or acid-suppression therapy. However, published results are conflicting and few studies have focused on the relationship between *H. pylori* infection and GM in the pathogenesis of duodenitis (4-11).

Clinically, we observed quite a few patients with endoscopic diffuse nodularity, which is independent of duodenal ulceration, in the duodenal bulb. This alteration may be a special type of chronic duodenitis. The purpose of the present prospective study was to investigate the association between *H. pylori* infection and GM in patients with diffuse nodular duodenitis.

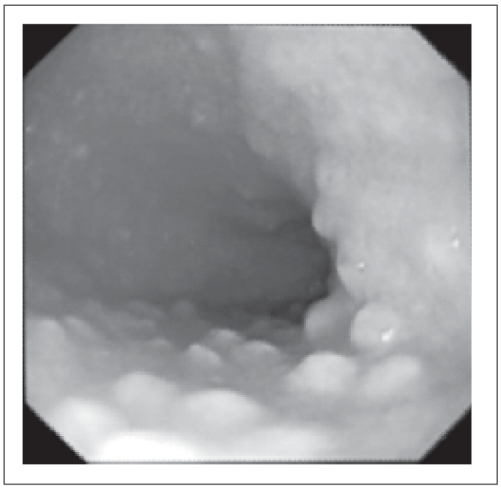

Figure 1. Diffuse nodularity in the duodenal bulb.

Patients and Methods

Patients

Between January 2002 and June 2005, 86 patients with endoscopically confirmed diffuse nodular duodenitis (Figure 1) were enrolled, including 50 patients (22 males; median age 49.0 years, range 23-75 years) with *H. pylori* infection and 36 patients (13 males; median age 52.6 years, range 22-76 years) without *H. pylori* infection. Forty patients (14 males; median age 51.6 years, range 20-78 years) with normal appearance of the duodenum were used as controls.

Patients were excluded who had 1) evidence of gastroduodenal malignancies, gastric ulcer, duodenal ulcer, or scar on gastroscopy; 2) liver, biliary, or pancreatic diseases on ultrasound examination; 3) received proton pump inhibitors (PPIs, such as omeprazole, lansoprazole, rabeprazole, and pantoprazole, etc.), bismuth, antibiotics, aspirin, or other non-steroidal anti-inflammatory drugs (NSAID) in the preceding 2 weeks; 4) Zollinger-Ellison syndrome or Crohn's disease involving the duodenum; 5) previous upper gastrointestinal surgery; 6) pregnancy, or 7) renal insufficiency or other severe concomitant illnesses. This study was approved by the Medicine Ethics Committee of Shanghai Renji Hospital and signed informed consent was obtained from all patients.

Clinical procedures

Patients with endoscopically confirmed diffuse nodular duodenitis were treated with anti-*H. pylori* triple therapy consisting of 20 mg omeprazole twice daily, 250 mg clarithromycin twice daily, and 400 mg metronidazole twice daily for one week when *H. pylori* infection was diagnosed either in the duodenal bulb or in the gastric antrum. A control endoscopy was performed 6 months after the anti-*H. pylori* treatment. The *H. pylori*-negative (both in the duodenal bulb

and in the gastric antrum) patients with diffuse nodular duodenitis received 20 mg omeprazole once daily for 6 months and a control endoscopy was performed 2 weeks after treatment. During the follow-up period after eradication treatment, intermittent short courses of hydrotalcite or sucralfate were prescribed to avoid symptoms and PPIs were avoided when possible.

Endoscopy and biopsy sampling

Endoscopic findings of duodenal morphology were defined according to the criteria of endoscopic duodenitis described by the Sydney classification (12), including the subjective assessment of severity as mild, moderate or severe. During each endoscopic examination, three antral biopsies were taken from the lesser and the greater curvature within 2-3 cm from the pylorus, and two duodenal biopsies were taken from the diffuse nodular lesion in the duodenal bulb. Among these biopsies, one antral specimen was used to detect *H. pylori* by the rapid urease test, and the others were used for histological assessment.

Histology

The biopsy specimens for histological examination were fixed in 10% formalin, embedded in paraffin on the oriented edge, and cut into 4-µm thick sequential sections. The tissue sections were then stained with hematoxylin and eosin for histological examination, with Alcian blue periodic acid-Schiff (AB/PAS) for identifying and assessing the extent of GM, and with Giemsa for *H. pylori* assessment.

The slides were evaluated by an experienced pathologist who was blind to clinical, endoscopic and other tests for *H. pylori*. Gastric antral and duodenal biopsy specimens were assessed according to the updated Sydney System (12). In each duodenal biopsy specimen, the infiltration of the duodenal mucosa by mononuclear cells (chronic inflammation) and polymorphonuclear leukocytes (neutrophilic activity) was graded as follows: 0, none; 1, mild; 2, moderate; 3, severe. GM was defined by the presence of surface epithelial cells containing PAS-positive neutral mucin in the duodenal bulb. The extent of gastric type epithelium in duodenal biopsy specimens was arbitrarily graded on a scale of 0-3 as follows: grade 0, no GM observed; grade 1, GM involving a few villi; grade 2, GM involving several villi, and grade 3, GM involving almost all villi (12). The lymphoid follicles were considered to be positive when aggregates of lymphocytes with a germinal center (secondary lymphoid follicles) or accumulations of lymphocytes and plasma cells without a germinal center (primary lymphoid aggregates) were observed. Villus atrophy was defined as flattening or widening of villi. *H. pylori* infection was diagnosed when the rapid urease test, hematoxylin and eosin stain, and Giemsa stain were all positive.

Statistical analysis

Data are reported as means ± SD. Differences were evaluated by the Fisher exact test, *t*-test, or Wilcoxon signed rank test. P values of <0.05 were considered significant.

Results

Helicobacter pylori status

Fifty patients (50/86, 58.1%) were *H. pylori* positive. Among the 76 patients who completed the study, 48 were *H. pylori* positive. After eradication treatment, 9 patients were still *H. pylori* positive.

Pre-treatment endoscopic appearance and histological findings

No common pathogenic factors, such as renal transplantation or duodenal parasitic

Table 1. Severity of diffuse nodular duodenitis in *Helicobacter pylori*-positive and *H. pylori*-negative groups before and after treatment.

	Severity of diffuse nodular duodenitis			
	None	Mild	Moderate	Severe
H. pylori-positive (N = 50)+	0	10	18	22
H. pylori-negative (N = 36)	0	10	16	10
Successful eradication of *H. pylori* (N = 39)				
Before eradication*	0	6	14	19
After eradication	5	5	13	16
PPI treatment (N = 28)				
Before treatment**	0	7	12	9
After treatment	4	8	8	8

+P > 0.05 compared with the *H. pylori*-negative group; *P > 0.05 compared with the group after *H. pylori* eradication; **P > 0.05 compared with the group after treatment with proton pump inhibitors (PPI; Wilcoxon signed rank test).

Table 2. Extent of duodenal gastric metaplasia in the *Helicobacter pylori*-positive and *H. pylori*-negative groups before and after treatment.

	Extent of duodenal metaplasia			
	Grade 0	Grade 1	Grade 2	Grade 3
Successful eradication of *H. pylori* (N = 39)				
Before eradication+**	11	4	10	14
After eradication	26	6	4	3
PPI treatment (N = 28)				
Before treatment**	13	5	6	4
After treatment	16	7	5	0

Grade 0, no gastric metaplasia observed; grade 1, gastric metaplasia involving a few villi; grade 2, gastric metaplasia involving several villi; grade 3, gastric metaplasia involving almost all villi.
+P = 0.032 compared with the group before proton pump inhibitors (PPI) treatment; *P = 0.0001 compared with the group after eradication of *H. pylori*; **P > 0.05 compared with the group after treatment with PPI (Wilcoxon signed rank test).

Table 3. Post-treatment histological changes of diffuse nodular duodenitis in the *Helicobacter pylori*-positive and *H. pylori*-negative groups.

Histological alterations	Post-treatment histological changes		
	Successful eradication of *H. pylori* (N = 39)	Failure of eradication of *H. pylori* (N = 9)	*H. pylori* negative (after PPI treatment) (N = 28)
Gastric metaplasia	13/28 (46.4%)+	6/6 (100%)	12/15 (80%)
Lymphoid follicles	0/26*	6/6 (100%)	5/8 (62.5%)
Villus atrophy	16/39 (41.0%)*	9/9 (100%)	14/15 (93.3%)
Goblet cell decrease	0/25*	6/6 (100%)	8/8 (100%)
Ectopic gastric mucosa	0	0	6/6 (100%)

PPI = proton pump inhibitors.
+P = 0.033, *P < 0.001 compared with the *H. pylori*-negative group (Fisher exact test).

infestation, were present in patients with nodular duodenitis. There was no significant difference in the severity of endoscopic nodular duodenitis between the *H. pylori*-positive and -negative groups (P = 0.144, Table 1).

GM was detected in 49 of the 86 patients (57.0%). The prevalence of GM, villus atrophy, goblet cell reduction, and lymphoid follicles was significantly higher in patients with *H. pylori* infection than in patients without *H. pylori* infection (P < 0.05 for all). The extent of GM was also greater in *H. pylori*-positive patients than that in *H. pylori*-negative patients (P = 0.032, Table 2). Furthermore, different degrees of chronic duodenal inflammation (average score, 3.4 ± 1.3) and neutrophilic activity (average score, 2.3 ± 1.9) were found in most of the patients with nodular duodenitis.

Only mild duodenal chronic inflammation (average score 0.8 ± 1.0) was found in 30 of 40 control patients with normal appearance of the duodenum. The values were significantly lower than those in *H. pylori*-positive or -negative patients in the treatment group (both P < 0.0001). No other histological alterations, including GM, were found in this group.

Post-treatment endoscopic appearance and histological changes

Seventy-six patients completed the study, including 48 patients with *H. pylori* eradication treatment (successful in 39) and 28 patients with PPI treatment. Neither the successful eradication treatment nor PPI treatment could improve the endoscopic appearance of nodular duodenitis (both P > 0.05, Table 1).

Six months after successful eradication of *H. pylori*, both the values of chronic inflammation and neutrophilic activity were significantly decreased (2.2 ± 1.2 *vs* 4.0 ± 1.5, P < 0.0001, and 0.1 ± 0.3 *vs* 3.8 ± 1.5, P < 0.0001, respectively). Furthermore, the

extent of duodenal GM was significantly reduced (P = 0.0001, Table 2), and regression of histological alterations was achieved in most or all patients (Table 3).

However, no significant change in histological findings, including GM, was found in *H. pylori*-negative patients on PPI treatment or in patients with persistent *H. pylori* infection after eradication treatment (Table 3).

Discussion

An association between GM, *H. pylori* infection and duodenitis has been reported (13-15). GM of the duodenum is characterized by the metaplastic replacement of the normal duodenal epithelial cells with those displaying a phenotype similar to that of mucus-secreting cells of the gastric mucosa. It resembles gastric foveolar epithelium in many respects, including *H. pylori* colonization (16,17). It has been suggested that the presence of GM may create a suitable environment for *H. pylori* colonization in the duodenum, resulting in chronic duodenitis (13,14,17,18). The development of metaplastic tissue is a necessary prerequisite for *H. pylori* colonization because the bacterium may survive in the gastric mucosa but it cannot grow on normal duodenal epithelium (13,16,18). When spread to the duodenal mucosa, *H. pylori* is believed to exert a cytotoxic effect on mucosal cells. The inflammatory injury to duodenal mucosa by *H. pylori* may eventually lead to the development of further GM (13,14,19). *H. pylori* infection was confirmed to be one of the independent risk factors of GM (20), and an inductive role of *H. pylori* in the development of GM was suggested recently (21).

However, there are conflicting reports concerning the relationship between the extent of GM and *H. pylori* infection. It has been reported that neither the prevalence nor the extent of GM was affected by *H. pylori* status (5,6,9,22). In contrast, some studies found such a relationship between the extent of GM in the duodenum and the amount of *H. pylori* in the gastric antrum or in the duodenal bulb (3,4,13,17). Our study showed that both the presence and the extent of GM in nodular duodenitis are related to the presence of *H. pylori* infection.

There are also conflicting reports as to whether the extent of GM decreases after eradication of *H. pylori*. Some studies have shown no decrease in the extent of GM after eradication of *H. pylori* (5-7,9-11), whereas a significant reduction in the extent of GM was demonstrated in others (4,8). In agreement with the latter reports, the results of the present study showed that the extent of GM significantly decreased and complete regression occurred in more than half (15/28) the patients 6 months after eradication of *H. pylori.* In addition, the patients with successful eradication of *H. pylori* show a significantly higher prevalence of GM regression than those with no eradication. These findings further confirm the important contributory role of *H. pylori* infection in the development and persistence of GM.

In addition to *H. pylori* infection, it was speculated that the presence of duodenal GM is most likely caused by duodenal injury or high acidity (14,15), and is considered to be a protective mechanism to excess acid (23). But long-term acid inhibition treatment with H_2-receptor antagonists could not decrease the extent of GM (5). It was shown in another study that acid suppression alone produced a 43% reduction in GM, similar to the effect of *H. pylori* eradication. The authors concluded that the extent of GM was partly due to *H. pylori* and partly to acid (4). In the present study, only 20% regression in GM could be achieved with long-term acid inhibition treatment alone in patients without *H. pylori* infection. However, the results of PPI treatment should be interpreted with caution because the acidity levels were not evaluated. This aspect deserves further investigation.

Diffuse nodular duodenitis is a special

type of chronic duodenitis. Up to now, we know little about its pathogenesis. It was speculated that the appearance of endoscopic findings of duodenitis may result from *H. pylori* infection or from an acid-pepsin attack and is usually accompanied with some histopathologic abnormalities, including GM (17). However, few studies had focused on the association between the appearance of duodenitis and *H. pylori* infection. It has been reported that no significant difference exists in the severity of endoscopic duodenitis between *H. pylori*-positive and -negative patients, and successful eradication of *H. pylori* did not lead to any change in endoscopic appearance (9). In agreement with this finding, we found that neither the eradication of *H. pylori* nor the acid suppression treatment could change the appearance of endoscopic nodular duodenitis in a significant manner.

In conclusion, the present results suggest that *H. pylori* infection is related to the extent of GM in the duodenum, but not to the presence of diffuse nodular duodenitis.

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