ORIGINAL

Long-term follow-up of gastric metaplasia after eradication of *Helicobacter pylori*

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Abstract : Backgrounds and Aims : There is no commonly accepted view concerning changes in gastric metaplasia after the eradication of *Helicobacter pylori*. The aim of this study was to evaluate the long-term course of gastric metaplasia after the eradication of this bacterium.

Methods : The subjects were 59 patients with duodenal ulcer who were positive for *Helicobacter pylori*. Forty patients were classified as the eradication group. Gastric metaplasia was endoscopically and histologically evaluated before and after eradication of this bacterium. The follow-up period was 2-7.1 years. In the other 19 patients in the non-eradication group, gastric metaplasia was evaluated before and after treatment of the ulcer. Gastric metaplasia was evaluated in terms of its extent and type in all patients.

Results : Gastric metaplasia showed the incomplete type before eradication but changed to the complete type after eradication, which persisted for a long period. The extent of gastric metaplasia increased after eradication. In the non-eradication group, gastric metaplasia infrequently changed to the complete type during the scarring period of ulcer.

Conclusion : Gastric metaplasia changed to the complete type after the eradication of *Helicobacter pylori*, which persisted for a long period. J. Med. Invest. 50 : 48-54, 2003

Keywords **:** *gastric metaplasia, Helicobacter pylori, duodenal ulcer, eradication*

INTRODUCTION

In 1964, James (1) observed a high incidence of gastric metaplasia (GM) in patients with duodenal ulcer, and suggested its role in the defense against high gastric acidity. Since the discovery of *Helicobacter pylori* (*H. pylori*) in 1983 (2), a close association between this bacterium and duodenal ulcer has been suggested. However, no consistent results or conclusions have been obtained concerning changes in GM after *H. pylori* eradication.

We classified the morphology of GM into 3 types according to the amount of mucus in metaplastic cells and evaluated the long-term course of GM after *H. pylori* eradication.

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METHODS

Patients

The subjects were 59 *H. pylori*-positive patients with active duodenal ulcers who were undergoing endoscopic examination. Patients who had received antibiotics, acid suppression treatment, or corticosteroids in the previous month or who were receiving nonsteroidal anti-inflammatory drugs were excluded. Patients in whom gastric surgery was performed, or endoscopic biopsy was contraindicated were also excluded.

In 40 patients (25 males and 15 females ; median age, 51 years ; age range, 33-72 years), *H. pylori* could be eradicated by triple drug therapy with lansoplazole, amoxicillin, and metronidazole (eradication group). In the other 19 patients (13 males and 6 females ; median age, 48 years ; age range, 26-70 years), *H. pylori* were not eradicated (non-eradication group).

Clinical procedures

The eradication group received 1.5 g/day of amoxicillin and 500 mg/day of metronidazole for 1 week, and 30 mg/day of lansoplazole for 6 weeks after initial endoscopic examination, followed by consecutive administration of an H_2-receptor antagonist at the standard dose for 4 weeks.

The non-eradication group received 30 mg/day of lansoplazole for 6 weeks after initial endoscopy and, in addition, received the same regimen of an H_2-receptor antagonist as the successful eradication group.

At the initial endoscopy, two paired biopsies were obtained from the greater curvature of the gastric antrum as well as of the gastric corpus in all patients in both groups. Of the two paired biopsies, one was used for the rapid urease test, and the other was placed in 10% buffered formalin for histological examination to confirm *H. pylori* infection.

Two duodenal biopsies were performed from the ulcer margin at the same time and also placed in 10% buffered formalin and processed for the histological examination of GM.

All patients in both groups underwent endoscopy again after treatment for 10 weeks. Gastric biopsies were repeated, being obtained from a topographical site similar to that in the initial endoscopy. Two duodenal biopsy specimens were obtained from the center of the scar.

The 40 patients in the eradication group were followed up for 2.0-7.1 years (mean, 3.6 years) after confirmation of eradication to evaluate the course of duodenal ulcer and examine for *H. pylori*. Endoscopy was performed once-7 times (mean, 2.9 times) after the confirmation of *H. pylori* eradication. At each endoscopy, biopsy specimens were obtained from the stomach and the center of the duodenal ulcer scar by the above-described method. In patients with recurrence, biopsy specimens were obtained from the ulcer margin in the same way as in the initial endoscopy.

Of patients who could be followed up in the non-eradication group, 6 did not show recurrence. In the 6 patients, biopsy specimens were obtained from the greater curvature of the gastric antrum and corpus and the center of the duodenal ulcer scar, and *H. pylori* and GM were examined.

The eradication of *H. pylori* was confirmed by a negative biopsy urease test and negative results of histological examination.

Informed consent about the eradication of *H. pylori* and endoscopic biopsy was obtained from all patients who entered this study.

Histological methods

Duodenal and gastric sections were routinely processed, cut at 3 μm, and stained with hematoxylin-eosin, alcian blue periodic acid Schiff, and Giemsa stain. Duodenal sections stained with hematoxylin-eosin and alcian blue periodic acid Schiff were used to identify and assess the extent and type of GM. Giemsa stain was used to identify the presence of *H. pylori* in areas of GM. Hematoxylin-eosin staining of gastric biopsy specimens was performed for histological examination for gastritis, and Giemsa stain was used for the detection of *H. pylori*.

The extent of GM was classified according to our previously reported method : (3-5) grade 0, absence of GM ; grade 1, GM involving a few villi ; grade 2, GM involving several villi ; and grade 3, GM involving almost all villi.

GM was classified into 3 types according to the amount of mucus in the metaplastic cells : complete, intermediate, and incomplete (5). The complete type of GM was characterized by tall mucin-abundant cells (Fig. 1). The incomplete type of GM was dark with cuboidal cells poor in mucin (Fig. 2). The intermediate type was between the two types.

When the grade differed between the two specimens from the same subject, the higher grade was

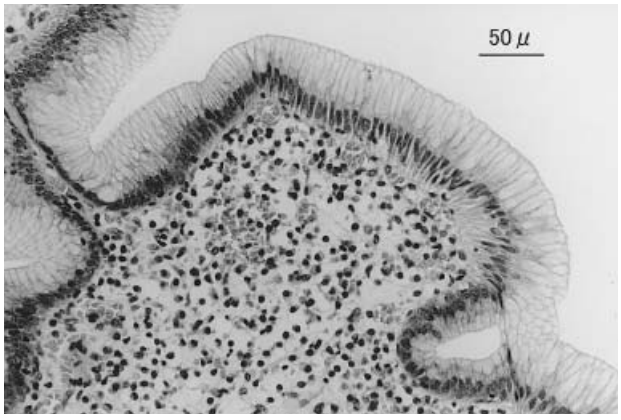

Fig. 1. Complete-type gastric metaplasia. Tall columnar metaplastic cells were abundant in mucin (hematoxylin and eosin, ×75).

regarded as the grade for that subject.

Statistics

Statistical analysis was performed using Wilcoxon's signed rank test. P values < 0.05 were considered significant.

RESULTS

Changes in GM in the eradication group

Table 1 shows changes in the type of GM before and after 10 weeks of treatment in the 40 patients with duodenal ulcer in the successful eradication group. Before eradication (active stage of duodenal ulcer), the incomplete type was observed in 35 of the 40 patients and the intermediate type in the other 5. After *H. pylori* eradication (scarring stage), the complete type was observed in 39 patients and the intermediate type in the other. Thus, the incomplete type of GM was frequently observed before eradication, but the complete type was primarily observed after eradication ($p<0.0001$).

Before eradication, the extent of GM was graded as 0 in none of the 40 patients, 1 in 13, 2 in 19, and 3 in 8. After eradication, grade 0 was observed in none of the 40 patients, grade 1 in none, grade 2 in 5, and grade 3 in the other 35 (Table 2). The extent of GM after eradication was greater than that before eradication ($p<0.0001$).

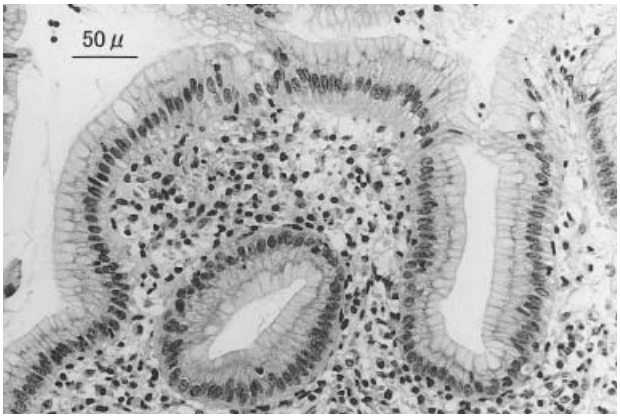

Fig. 2. Incomplete-type gastric metaplasia. Metaplastic cells were smaller and contained a lower amount of mucin (hematoxylin and eosin, ×75).

Long-term course of GM in the successful eradication group

Fig. 3 shows the course of GM after *H. pylori* eradication in the 40 patients who were followed up for 2 years or more after eradication. In most patients showing a change to the complete type after eradication, this state was maintained for a long period. However, in 5 patients, the complete type changed to the intermediate type during the follow-up period. In 3 patients who became *H. pylori*-positive again, GM changed to the incomplete type, and the extent of GM also decreased. Of the other 37 patients who were consistently *H. pylori*-negative, 15 showed a decrease in the extent of GM 1.5-4.5 years after eradication. However, in some patients, grade 3 GM persisted for 3 to 7 years.

Changes in GM in the non-eradication group

Table 3 shows GM types before (active stage of duodenal ulcer) and after (scarring stage) treatment in the 19 patients with duodenal ulcer in the non-eradication group. Before treatment, the complete type was observed in none of the 19 patients, intermediate type in 3, and the incomplete type in 16. After treatment for 10 weeks, the complete type was observed in 6 patients, intermediate type in 6,

Table 1. Type of gastric metaplasia before and after eradication of *H. pylori* (successful eradication group)

	Complete	Intermediate	Incomplete
Before eradication (n=40)	0	5	35
After eradication (n=40)	39	1	0

P<0.0001

Table 2. Extent of gastric metaplasia before and after eradication of *H. pylori* (successful eradication group)

	Grade 0	Grade 1	Grade 2	Grade 3
Before eradication (n=40)	0	13	19	8
After eradication (n=40)	0	0	5	35

P<0.0001

and incomplete type in 7. The incomplete type was frequently observed in the active stage while the complete type increased, and the incomplete type decreased in the scarring stage (p=0.0024).

The extent of GM before treatment was graded as 1 in 7 patients and 2 in 12, and that after treatment was graded as 2 in 4 patients and 3 in 15 (Table 4). Thus, the extent of GM in the scarring stage was greater than that in the active stage (p< 0.0001).

Course of GM in patients without ulcer recurrence in the non-eradication group

Fig. 4 shows the course of GM in 6 patients without ulcer recurrence during the follow-up period in the non-eradication group. The follow-up period

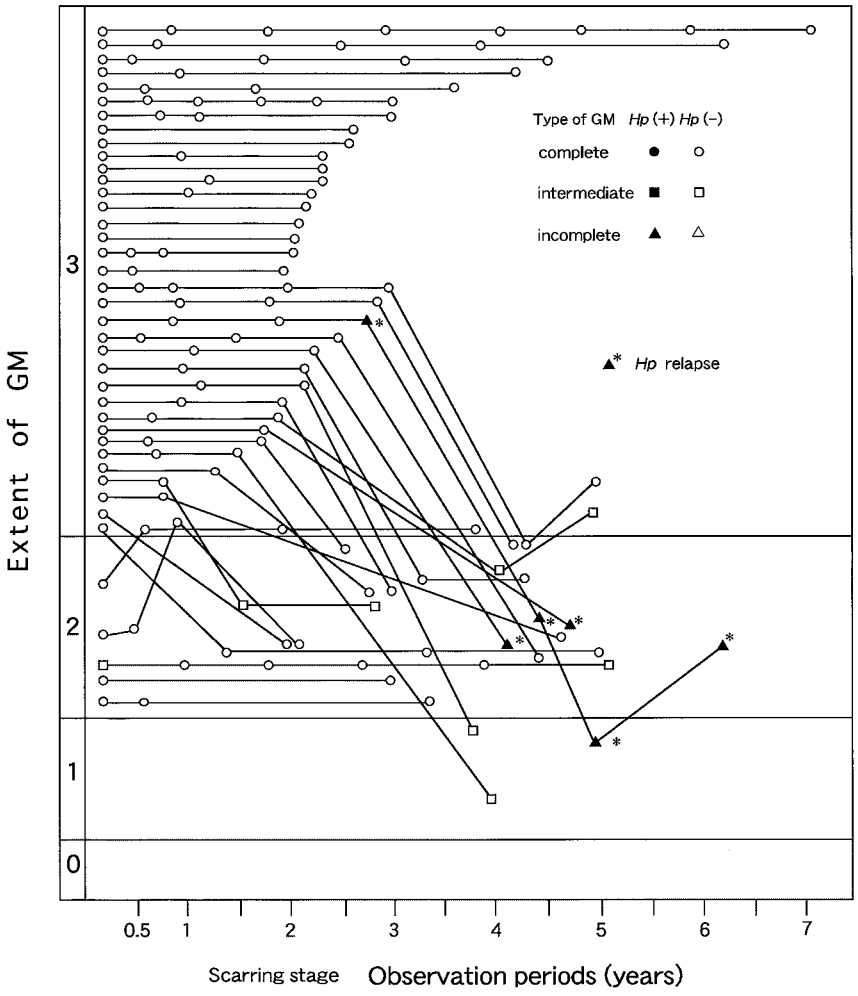

Fig. 3. Changes in gastric metaplasia after successful eradication.

Table 3. Type of gastric metaplasia in the active stage and scarring stage (non-eradication group)

	Complete	Intermediate	Incomplete
Active stage (n=19)	0	3	16
Scarring stage (n=19)	6	6	7

P<0.0024

Table 4. Extent of gastric metaplasia in the active stage and scarring stage (non-eradication group)

	Grade 0	Grade 1	Grade 2	Grade 3
Active stage (n=19)	0	7	12	0
Scarring stage (n=19)	0	0	4	15

P<0.0001

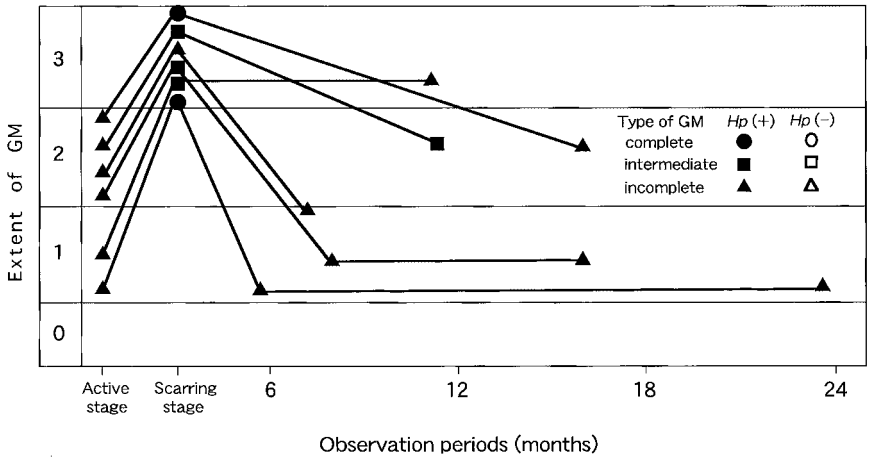

Fig. 4. Changes in gastric metaplasia in patients without recurrences (non-eradication group).

ranged from 7 to 23.5 months (mean, 14.3 months). Before treatment (active stage), all the 6 patients showed the incomplete type. After 10 weeks of treatment (scarring stage), the complete type was observed in 2 patients, intermediate type in 3, and the incomplete type in 1. The extent of GM before treatment was graded as 1 in 2 patients and 2 in 4, but that after treatment was graded as 3 in all the 6 patients. Follow up examination showed a change to the incomplete type again and a decrease in the extent of GM in most patients despite the maintenance of the ulcer scarring stage.

Thus, the non-eradication group showed a lower incidence of complete type GM in the scarring stage than the successful eradication group. In addition, the extent of GM, which increased in the scarring stage, decreased after a short period.

DISCUSSION

GM has been considered to be a protective response to exposure to high acidity in the duodenal bulb (1, 6-8). In the presence of *H. pylori* infection in the stomach, *H. pylori* harbors in GM areas, which causes duodenitis (9), leading to duodenal ulcer (8).

Concerning changes in GM after *H. pylori* eradication for duodenal ulcer, Noach *et al.* (10) and Harris *et al.* (11) reported no significant differences between the prevalence and extent of GM before eradication and those after eradication. Conversely, Khulusi *et al.* (12) observed a 42% reduction in the extent of GM after eradication. Therefore, no consistent findings have been obtained. We previously reported that GM presented a well-developed appearance with abundant intracellular mucus after successful eradication and remained in this condition for a long period (4).

Previous studies on GM have evaluated the prevalence and extent of GM (8) but rarely the properties of GM. Since there are only a few *H. pylori*-negative patients with duodenal ulcer, we previously evaluated differences in the properties of GM (5) between the presence and absence of *H. pylori* infection in patients with endoscopic duodenitis (13). GM showed the complete type in *H. pylori*-negative patients with endoscopic duodenitis but the incomplete type in *H. pylori-positive* patients. These findings suggested the importance of the consideration of not only the prevalence and extent of GM but also its type (complete or incomplete) that represents the maturity of *H. pylori* (5).

In this study, most patients with duodenal ulcer showed the incomplete type before eradication but a change to the complete type after eradication and the persistence of the complete type for a long period. However, the patients with recurrence of *H. pylori* showed a change to the incomplete type again during the follow-up period. In the non-eradication group, GM changed to the complete type with healing of the ulcer in some patients but remained the incomplete or intermediate type in others. In addition, most patients with a change to the complete type after treatment showed a change to the incomplete type again and a decrease in the GM extent grade during the follow-up period. These findings were in contrast to the persistence of the complete type in the eradication group.

There have been a few studies on the long-term course of GM after *H. pylori* eradication, and the results of these studies have been inconsistent (4, 10-12, 14). In this study, long-term follow up (maximum, 7.1 years) of GM revealed the persistence of grade 3 GM extent in most patients until about 2 years after eradication but a subsequent decrease

in the grade in some patients. Kim *et al.* (14) reported that the prevalence and extent of GM did not change until 1 year after *H. pylori* eradication but decreased slightly 4 years after eradication.

Studies have shown a decrease in acid output after *H. pylori* eradication in patients with duodenal ulcer, but the observation period in these studies was relatively short (6-12 months after eradication) (15-18). The development of GM is considered to be closely associated with gastric high acidity (1, 19, 20). However, the decrease in acid secretion after eradication may not be adequate to reduce the extent of GM during only the 2-year period after eradication. The results of this study and the study by Kim *et al.* (14) suggest that a decrease in acid output enough to reduce the extent of GM occurred 2-4 years after eradication in some patients. However, some patients showed the persistence of grade 3 GM for a long period such as 7.1 years. In these patients, acid output that induces GM may have been still sustained. However, even in patients with persistent high acidity, since the complete type of GM containing abundant mucus persists in the environment after *H. pylori* eradication, the defense against acid may be adequate, and ulcer may not recur (4).

The importance of GM in duodenal ulcer may be as follows (Fig. 5). GM develops in the healing process of duodenal erosion and ulcer (3, 19) as a defense mechanism against high acidity (1, 6-8). In an *H. pylori*-positive environment, GM shows the incomplete type due to invasion and damage by *H. pylori*. Since the defense against high acidity may be decreased in mucosal areas with incomplete type GM poor in mucus and marked *H. pylori*-induced inflammation, ulcer may develop in these areas.

In the healing stage of ulcer, an increase in the extent of GM and complete type GM are observed in some patients. However, in a consistently *H. pylori*-positive environment, GM decreases in its extent and changes to the incomplete type again due to *H. pylori* invasion, and ulcer recurrence is repeated during the persistence of high acidity (4).

In patients who are *H. pylori*-negative or after eradication, complete type GM rich in mucus is observed, and mucosal inflammation is also mild. Therefore, the defense against high acidity is adequate, and ulcer may not develop or recur.

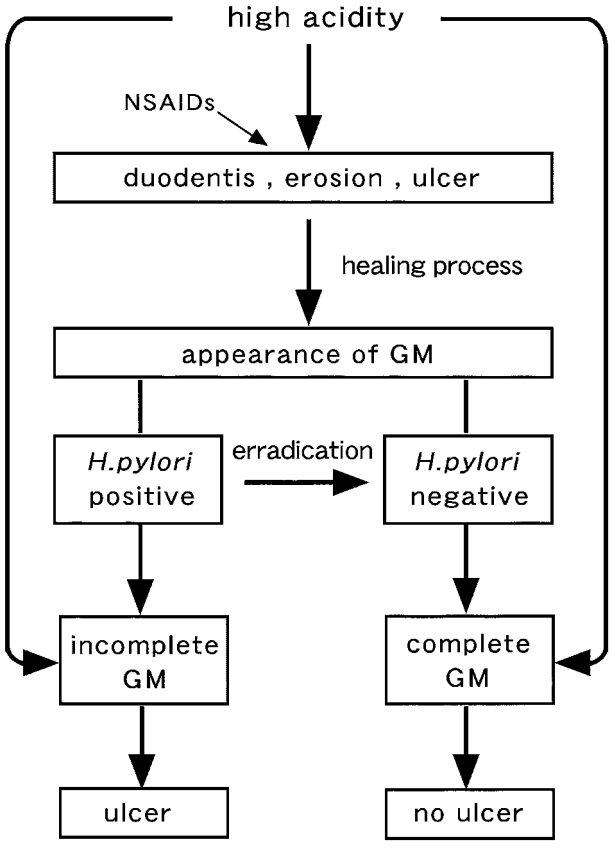

Fig. 5. Relationship between the appearance of gastric metaplasia and *Helicobacter pylori*.

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