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Antralization at the edge of proximal gastric ulcers: Does *Helicobacter pylori* infection play a role?

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Abstract

AIM: To determine the prevalence of antralization at the edge of proximal gastric ulcers, and the effect of *H. pylori* eradication on the mucosal appearances.

METHODS: Biopsies were taken from the antrum, body and the ulcer edge of patients with benign proximal gastric ulcers before and one year after treatment. Gastric mucosa was classified as antral, transitional or body type. *H. pylori* positive patients received either triple therapy, or omeprazole.

RESULTS: Patients with index ulcers in the incisura, body or fundus (n=116) were analyzed. Antral-type mucosa was more prevalent at the ulcer edge in *H. pylori*-positive patients than *H. pylori*-negative patients (93 % *vs* 60 %, OR=8.95, 95 %CI: 2.47-32.4, P=0.001). At one year, there was a significant reduction in the prevalence of antralization (from 93 % to 61 %, P=0.004) at the ulcer edge in patients with *H. pylori* being eradicated. However, there was no difference in the prevalence of antralization at the ulcer edge in those with persistent infection.

CONCLUSION: *H. pylori* infection is associated with antralization at the edge of proximal gastric ulcers, which may be reversible in some patients after eradication of the infection.

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INTRODUCTION

Peptic ulcer disease is common, and is associated with considerable mortality due to complications such as bleeding and perforation[1]. *H. pylori* infection is now recognized to be a major cause for peptic ulcer, accounting for up to 90 % of duodenal ulcer cases and 80 % of gastric ulcer cases, with the use of non-steroidal anti-inflammatory drugs being another major cause[2-4]. While gastric metaplasia in duodenum has been identified to be an important morphopathological change in the development of *H. pylori*-associated duodenal and prepyloric ulcer[5-7], the mucosal morpho-pathogenesis of gastric ulcer, which occurs predominantly along the body-antrum transitional zone (particularly at the gastric incisura), remains unclear. Previous studies have observed a stem-cell-derived "ulcer-associated cell lineage" (UACL) at the sites of chronic gastrointestinal ulceration, commonly found in the borders of Crohn' s ulcers in small bowel, and in gastroduodenal ulceration[8-11]. In the literature, UACL was usually described as pseudopyloric (or pyloric) metaplasia, because it has morphological similarities to pyloric glands[8, 9], and similar changes can occur in other tissues, such as gall bladder, bile ducts, and pancreatic ducts, often associated with malignant transformation of these tissues[12-16]. In the stomach, pseudopyloric metaplasia is specifically defined as a replacement of specialized glands by mucous-secreting glands in the gastric body or at the body-antrum junction[17], a concept identical to "antralization" as described in our previous studies[18, 19].

In a previous study, we have demonstrated that in the absence of *H. pylori* infection, the gastric incisura mucosa belongs to either body-type or transitional type in most (82 %) individuals, suggesting that normal incisura mucosa is histologically distinct from the antral mucosa, but more homologous to the body and fundus mucosa[18]. However, *H. pylori* infection is associated with the presence of antral (pyloric)-type mucosa in the proximal stomach (i.e. gastric incisura, body and fundus), indicating that *H. pylori* infection may be a causal factor for antralization of the proximal stomach[18]. Thus, it is conceivable that *H. pylori*-induced antralization may play an important pathogenic role in proximal gastric ulceration, and eradication of *H. pylori* infection may reverse antralization to normal transitional or body type mucosa, and thus reduce the risk for ulcer relapse. Therefore, the present study was carried out to determine the prevalence of antralization at the edge of proximal gastric ulcer in relation to *H. pylori* infection, and the effect of *H. pylori* eradication on the mucosal appearances.

MATERIALS AND METHODS

Patients

One hundred and sixteen patients with newly diagnosed uncomplicated benign-looking proximal gastric ulcers (>5 mm in diameter and >1 mm in depth) at the Endoscopy Unit of Department of Medicine, Queen Mary Hospital were included in the study. The location of gastric ulcers and demographic and clinical characteristics of these patients were summarized in Table 1. Exclusion criteria at entry included patients who had been taking aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) over the past year, or taking antibiotics, H_2 receptor blockers, bismuth or proton pump inhibitors in the

preceding 4 weeks, patients with previous gastric surgery, and those with a histological diagnosis of gastric carcinoma or lymphoma.

Informed written consent was obtained from all patients who participated in the trial. This project was approved by the Ethics Committee of the University of Hong Kong.

Table 1 The demographic clinical characteristics of the patients initially recruited, according to the location of gastric ulcers (n=116)

	Ulcer location		
	Incisura (n=91)	Body (n=23)	Fundus (n=2)
Age (mean ±SD)	59.5±13.3	69.3±10.2	51.0±11.2
Gender (male/female)	60/31	17/6	2/0
Smoking (yes/no)	44/46	11/12	1/1
H.pylori status (positive/negative)	81/10	19/4	1/1

Diagnosis of H. pylori infection

During the first endoscopy, three biopsies were taken at the gastric antrum within 3 cm of the pylorus at the lesser curvature, two at the midway between the pylorus and cardioesophageal junction at the greater curvature, and four from the edge of gastric ulcer. When the ulcer was present in the body, the body biopsies were taken at least 3 cm apart from the ulcer. One antral biopsy was used for a rapid urease test (RUT) and the rest were sent for the detection of *H. pylori* infection and histological examination after haematoxylin & eosin (H&E) staining. All patients then received a ^{13}C-urea breath test following a standard protocol measured by an isotope ratio mass spectrometer[20]. The definition of *H. pylori* infection in this study required that at least two of the three tests (the RUT, histology and ^{13}C-urea breath test) were positive. The absence of *H. pylori* infection required all three tests to be negative. This definition was used as the "gold standard" in this study.

Histological examination

Slides were read by experienced pathologists who were blinded to all clinical and endoscopic information, including the RUT results. The mucosa of gastric biopsies taken from different sites was classified as antral (mucous-secreting or pyloric) type, body (acid-secreting or oxyntic) type or transitional (junctional) type according to the definitions set out in the updated Sydney system[21]. The characteristic feature of antral-type mucosa was the presence of coiled and branching antral glands, which were lined by mucus cells that were interspersed with endocrine cells (chiefly G and D types), and a few parietal cells. The glands in body-type mucosa were straight tubes that constituted acid-producing parietal cells along with scattered mucus cells in their upper portion and mainly chief cells in their lower portion, with scattered argyrophilic endocrine cells. Transitional type mucosa was a mixture of the architectural features and cell types found in the antral and body type mucosae[21].

Treatment and endoscopy at one year

One hundred and one patients received triple therapy consisting of clarithromycin 250 mg, metronidazole 300 mg each given 4 times daily for 2 weeks and sucralfate 1 gm 4 times daily for 4 weeks (n=54), or acid suppression therapy consisting of omeprazole 20 mg daily for one year (n=47). Successful eradication was indicated if the rapid urease test, histological examination by H&E and Giemsa staining and ^{13}C-urea breath test were all negative at week 6 after treatment. 65 patients (male/female 44/21, age (mean±SD) 61.9±11.0 years) received either triple therapy (n=28), or omeprazole (n=37), with ulcers completely healed at 12 weeks. Upper endoscopy and ^{13}C-urea breath test were repeated at month 12. Gastric biopsies were obtained from the antrum, body and ulcer site (visible scar area in 47 of 53 (90.6 %) cases with a healed ulcer) or the edge of ulcer in 12 patients with relapsed ulcers, and assessed as described above. Successful eradication was indicated if the rapid urease test, histological examination by H&E and Giemsa staining and ^{13}C-urea breath test were all negative at week 6 or month 12 after treatment. The histological characteristics of these biopsies were compared with those biopsies taken at the first endoscopy. Histological improvement of gastric mucosa over the period of one year was defined as changes from antral to transitional or body, or from transitional to body-type, whereas worsening of gastric mucosa was defined as changes from body to transitional or antral, or from transitional to antral-type. An upper endoscopy and a ^{13}C-urea breath test were repeated at month 12 for 65 patients (male/female 44/21, age (mean±SD) 61.9±11.0 years) who had their ulcers completely healed 12 weeks after treatment. Gastric biopsies were obtained from the antrum, body and ulcer site (visible scar area) in 47 of 53 (90.6 %) cases with a healed ulcer or the edge of ulcer in 12 patients with relapsed ulcers, and assessed as described above. The histological characteristics of these biopsies were compared with those biopsies taken at the first endoscopy. Histological improvement of gastric mucosa over the period of one year was defined as changes from antral to transitional or body, or from transitional to body-type, whereas worsening of gastric mucosa was defined as changes from body to transitional or antral, or from transitional to antral-type.

Statistical analysis

The Chi-squared test (with Yates' correction if required), the Fisher's exact test or McNemar test was used for categorical variables, and odds ratios (OR) and 95 % confidence interval (CI) were estimated where appropriate. All tests were carried out using the SPSS system (version 10.0, SPSS Inc. Chicago, Illinois, USA). All P values calculated were two-tailed. The alpha level of significance was set at P<0.05.

RESULTS

The presence of antral-type mucosa in the gastric body and at the edge of proximal gastric ulcers

Of the 116 patients, 91 had the index ulcers at the incisura, 23 in the body and 2 in the fundus. Of these, 101 were *H. pylori*-positive and 15 were *H. pylori*-negative. All biopsies taken from the antrum showed antral-type mucosa. Overall, antral-type mucosa was present in the gastric body in 6 (5.2 %) patients and at the edge of proximal gastric ulcers in 103 (88.8 %) patients. Of *H. pylori*-positive patients 6 (5.9 %) had antral-type mucosa and 4 (4 %) had transitional type mucosa whereas all (100 %) of *H. pylori*-negative patients had body-type mucosa at the gastric body. Antral-type mucosa was present at the edge of proximal gastric ulcers in 93.1 % (94/101) of *H. pylori*-positive patients and 60 % (9/15) of *H. pylori*-negative patients (OR=8.95, 95 % CI: 2.47-32.4, χ^2=14.35, P=0.001) (Figure 1). In *H. pylori*-positive patients, 81 had ulcers at the incisura, 19 at the body and one at the fundus. In the presence of *H. pylori* infection, there was no difference in the prevalence of antral-type mucosa at the ulcer edge at different gastric sites: 92.6 % (75/81) at the incisura, 94.7 % (18/19) at the body and 100 % (1/1) at the fundus. In *H. pylori*-negative patients, antral-type mucosa was present at the edges of ulcers in 70 % (7/10), 50 % (2/4) and 0 % (0/1) of patients when the ulcer occurred at the incisura, body and fundus, respectively.

Changes of gastric mucosa in the gastric body and at the edge of proximal gastric ulcers at one year

Of the 65 patients who were followed up for one year, 28 had *H. pylori* infection eradicated and 27 had persistent infection. Of the 12 patients with ulcers relapse, one (3.6 %) was from patients in whom *H. pylori* infection was eradicated and 11 (29.7 %) were from those with persistent infection (OR=11.4, 95 % CI: 1.38-94.9, χ^2=5.61, *P*=0.018).

There was a significant reduction in the prevalence of antral-type mucosa at both the gastric body (from 7.1 % to 0 %) and the gastric ulcer sites (from 92.9 % to 60.7 %, *P*=0.004, McNemar test) in patients in whom *H. pylori* infection was eradicated. However, there was no difference in the prevalence of antral-type mucosa when *H. pylori* infection was persistent (Figure 2).

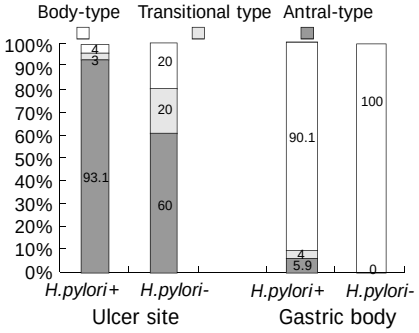

Figure 1 Prevalence of antral-type mucosa at the edge of proximal gastric ulcers and non-ulcerated gastric body in *H. pylori*-positive patients (*H. pylori*+, *n*=101) and those without *H. pylori* infection (*H. pylori*-, *n*=15).

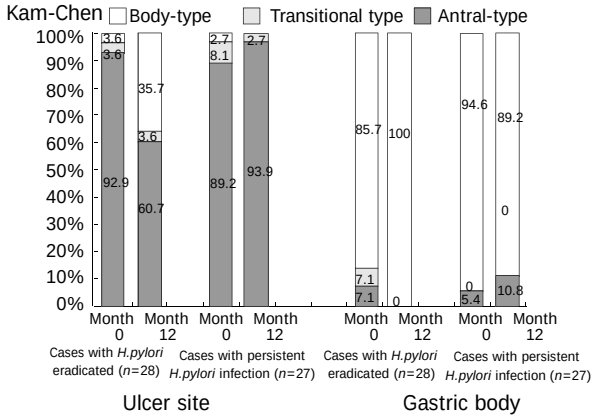

Figure 2 Presence of antral-type mucosa at the edge of proximal gastric ulcers and non-ulcerated gastric body in patients with *H. pylori* eradicated (*n*=28) and in those with persistent infection (*n*=37) before (month 0) and 12 months after treatment.

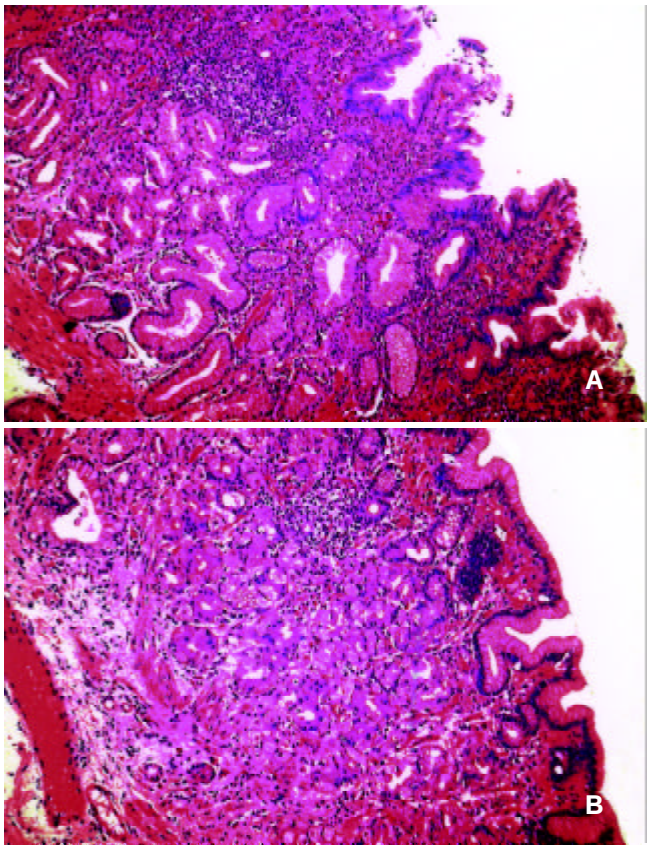

Figure 3 Gastric mucosa at the ulcer edge before and after eradication of *H. pylori* infection in the same patient. A, biopsy of the ulcer edge before *H. pylori* eradication showing antral-type gastric mucosa with severe active chronic inflammation; B, biopsy of the healed ulcer site after *H. pylori* eradication showing body-type gastric mucosa with presence of parietal and chief cells in the gastric glands and mild residual chronic inflammation. Haematoxylin & eosin (H&E) staining ×250.

Histological improvement of gastric mucosa was observed in 14 (21.5 %) patients; 3 at the gastric body, 9 at the ulcer site and 2 at both sites (Figure 3). Histological improvement of gastric mucosa at the ulcer sites was more common in patients in whom *H. pylori* was eradicated than those with persistent infection (35.7 % *vs* 2.7 %, OR=20.0, 95 % CI: 2.37-168.6, χ^2=12.35, *P*<0.001) (Table 2). When patients with relapsed ulcers were excluded, the association remained unchanged (37.0 % *vs* 3.8 %, OR=14.71, 95 % CI: 1.72-125.7, χ^2=8.87, *P*=0.003). Similarly, triple therapy was associated with a higher rate of histological improvement at the ulcer site, compared to omeprazole treatment (31.0 % *vs* 5.6 %, OR=7.65, 95 % CI: 1.50-39.0, χ^2=5.72, *P*=0.017). Gastric mucosa at the ulcer site was improved in more patients with cured ulcers than those

Table 2 Changes of gastric mucosa at the edge of proximal gastric ulcers and gastric body one year after treatment, in relation to post-treatment *H. pylori* status, treatment regimens, ulcer relapse and ulcer location (*n*=65)

	Mucosal type change (%)					
	Ulcer edge			Gastric body		
	Improvement[a] (*n*=11)	No change[b] (*n*=49)	Worsening[c] (*n*=5)	Improvement (*n*=5)	No change (*n*=58)	Worsening (*n*=2)
H. pylori infection						
Eradicated (*n*=28)	35.7[d]	64.3	0	14.3	85.7	0
Persistent (*n*=37)	2.7	83.8	13.5	2.7	91.9	5.4
Ulcer location						
Incisura (*n*=52)	15.4	76.9	7.7	5.8	90.4	3.8
Body (*n*=13)	23.1	69.2	7.7	15.4	84.6	0

[a], Improvement, antral-type (A)→transitional type (T), A→body-type (B), or T→B; [b], No change, A→A, T→T or B→B; [c], Worsening, T→A, B→A or B→T. [d], *P*<0.001, compared with persistent infection.

with relapsed ulcers, although the difference did not reach statistical significance (20.8 % *vs* 0 %, *P*=0.109). There was no difference in histological improvement between patients with ulcers at the body/fundus and those with ulcers at the incisura (23.1 % *vs* 15.4 %, OR=1.65, 95 % CI: 0.37-7.35, *P*=0.804) (Table 2). Age and gender were not associated with histological improvement (data not shown).

Overall, 7 (10.8 %) patients had worsened histology after treatment; 5 at the ulcer edge and the other 2 at the gastric body (Table 2). All of these patients had persistent *H. pylori* infection; 6 were treated with omeprazole and one with triple therapy. 3 (75 %) of these patients had ulcer relapsed.

DISCUSSION

In the present study, approximately 90 % of patients with proximal gastric ulcers had antral-type mucosa at the ulcer edge, and *H. pylori* infection was associated with a higher prevalence of antralization in the proximal gastric ulceration. Moreover, eradication of *H. pylori* infection resulted in histological improvement at the ulcer edge of 36 % of patients in 12 months, whereas the persistence of the infection was accompanied by worsening of histology (14 %). These findings suggest that *H. pylori* infection contributes to antralization, which may, in turn, play an important role in gastric ulceration.

H. pylori-associated antralization is believed to be a consequence of direct insults of chronic *H. pylori* infection, as a host defense and reparative response to the mucosal damage caused by organisms. As demonstrated in our previous study and in the present study, *H. pylori* infection is associated with antralization (or pseudopyloric metaplasia) at the gastric incisura and less frequently at the body and fundus[18]. It has been established that *H. pylori* infection induces apoptosis of gastric epithelial cells, and subsequently stimulates cell proliferation in the gastric mucosa[22]. Hanby *et al* reported that mucous neck cells formed an important cell lineage which secretes a series of peptides including the spasmolytic polypeptide, or trefoil family factor 2 (TFF-2) with luminal protective functions[23]. It has been suggested that pseudopyloric metaplasia occurs in the body glands as a result of hyperplasia of mucous neck cells, and represents a mucosal response to damage associated with *H. pylori* infection[18, 23]. Indeed, Schmidt *et al* reported that the spasmolytic polypeptide-expressing metaplastic (SPEM) lineage was closely associated with fundic *H. pylori* infection[24]. Thus, we propose that the hyperplastic mucous neck cells move both upwards and particularly downwards in the oxyntic tubule, replace the specialized parietal and chief cells, and create a mucous cell lineage. This process can occur focally, occupying a single oxyntic tubule, groups of tubules, or on a fairly massive scale with many tubules involved[25]. Eventually a mucous gland, which resembles pyloric glands, is formed, and thus antralization of proximal gastric mucosa follows. It is most likely that the weakened antralized mucosa in the proximal stomach is prone to be further damaged by *H. pylori*, resulting in ulceration even in the presence of subnormal acid production[26] Therefore, in the presence of persistent chronic infection with *H. pylori*, this defense and reparative mechanism probably facilitates rather than prevents the development of ulceration.

In the present study, eradication of *H. pylori* infection led to histological improvement, and persistent infection was associated with the development of antralization in the proximal stomach. These observations may have implications for the prevention of the development of gastric cancer, as we have previously reported that antralization of gastric incisura is strongly associated with precancerous lesions such as gastric atrophy and intestinal metaplasia[18]. It has been shown that the time-dependent progression of gastritis in grade (development of atrophy and intestinal metaplasia) and in extent (spreading of gastritis by pyloro-cardial extension) is correlated with the development of gastric cancer in the distal and angular stomach[27], and that atrophic gastritis and intestinal metaplasia progress and exhibit a cephaloid shift (i.e. pyloro-cardial extension) in chronic *H. pylori* infection[28]. Therefore, it is hypothesized that the initial events in gastric carcinogenesis occur at the junction of the oxyntic and antral mucosae, and it is the antral type mucosa that is prone to gastric atrophy and intestinal metaplasia, and expansion of antral mucosa towards the proximal stomach (either by pyloro-cardial extension or by differentiation) may be associated with an increased risk of developing intestinal metaplasia[29]. However, gastric atrophy and intestinal metaplasia are unlikely to regress after eradication of *H. pylori* infection although this is controversial[30-33]. On the other hand, the reversibility of antralization at the proximal gastric mucosa may provide a new hallmark in the chemoprevention of gastric cancer, although further studies on the role of antralization in gastric carcinogenesis are required. If the proposals of Schmidt *et al*[24] are confirmed, the prevention or reversal of SPEM might be critical.

Sampling error might account for the difference in improvement of gastric mucosa between patients with *H. pylori* eradication and those with persistent infection. For example, biopsies may be more correctly taken at the edge of active ulcers than healed ulcers. In most cases, ulcer scars are visible, which helps to improve the accuracy of the biopsy site.

Notably, the rate of antralization reached 60 % (9/15) for patients with proximal ulcers but without *H. pylori* infection, suggesting that certain other factors that result in gastric mucosal damage also lead to antralization and gastric ulceration. In the present study, there were no documented records on the causes of *H. pylori*-negative gastric ulcers, and thus we were unable to identify the potential factors that may lead to antralization. Some NSAID users who were unaware of NSAID use at entry might have been included. Previously, Lanas *et al* demonstrated that between 13 % and 22 % of patients with gastrointestinal bleeding and perforation who claimed not to have used aspirin had objective evidence of current aspirin intake[34, 35]. If this were the case in the present study, then NSAID use would account for proximal gastric ulcer in up to 3 of the 15 patients. Nevertheless, the significance of NSAID use and other factors in antralization of proximal stomach remains to be clarified.

In conclusion, *H. pylori* infection is associated with antralization at the edge of proximal gastric ulcers, which may be reversible in a proportion of patients after eradication of *H. pylori* infection. Antralization in the proximal stomach may play an important role in the pathogenesis of gastric ulceration.

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