

Adherence of *Helicobacter pylori* to Areas of Type II Intestinal Metaplasia in Korean Gastric Mucosa

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Abstract

The aim of this study was to examine whether *Helicobacter pylori* (*H. pylori*) attaches to areas of intestinal metaplasia in Korean patients. Gastric biopsy specimens with intestinal metaplasia from 8 gastric cancers, 24 gastric ulcers, 11 duodenal ulcers, and 57 chronic gastritis were examined. The specimens were stained with periodic acid-Schiff/alcian blue pH 2.5 and high-iron diamine/alcian blue pH 2.5 to identify the subtype of intestinal metaplasia, and then immunohistochemical stain was done with rabbit anti-*H. pylori* polyclonal antibody. In 17 patients, *H. pylori* attached to areas of type II intestinal metaplasia. All areas of intestinal metaplasia showing adherence contained sialomucin, and *H. pylori* was not detected in the areas of intestinal absorptive cells and sulfomucin-containing metaplastic cells.

Key Words: *Helicobacter pylori*, intestinal metaplasia, stomach

INTRODUCTION

H. pylori infection induces active inflammation with neutrophilic infiltration and also elicits chronic inflammation with infiltration of lymphocytes, macrophages/monocytes, and plasma cells in the lamina propria of gastric mucosa.¹ These neutrophils and macrophages/monocytes produce oxygen-free radicals that could cause DNA damage to adjacent cells.² Mutation of the DNA in stem cells of the gastric isthmus induced by oxygen-free radical damage could lead to intestinal metaplasia or atrophy.³ The fact that *H. pylori* is frequently undetectable in advanced atrophic metaplastic gastritis despite serological evidence of infection has prompted speculation that intestinal metaplasia may represent a mechanism that eliminates the bacteria.^{4,5}

Many investigators have believed that *H. pylori* specifically attaches to gastric epithelial cells.⁵⁻⁷ While conducting a study to examine cell proliferation and

apoptosis of *H. pylori*-infected antral epithelial cells in upper gastrointestinal diseases, we found that *H. pylori* was present in areas of intestinal metaplasia. Thereafter, we selected the gastric biopsy tissues showing extensive intestinal metaplasia in order to examine whether *H. pylori* attaches to areas of intestinal metaplasia.

CASE REPORT

Gastric antral biopsy specimens with intestinal metaplasia were obtained from 8 gastric cancers, 24 gastric ulcers, 11 duodenal ulcers, and 57 chronic gastritis from routine files in the Department of Pathology, Dongguk University, Kyongju Hospital from March 1996 through April 1998. All the specimens were infected with *H. pylori*. Sixty-five male patients and 35 female patients were studied. Their ages ranged between 23 and 74 years (mean \pm SD = 53.3 \pm 12.7 years).

Sections were initially stained with hematoxylin-eosin (H&E) and periodic acid-Schiff for routine histology. Gastric antral biopsy specimens from the area of intestinal metaplasia were obtained, and two additional sections were stained with periodic acid-Schiff/alcian blue pH 2.5 and high-iron diamine/alcian blue pH 2.5 to identify the subtype of intestinal metaplasia. One additional section was immunohistochemi-

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cally stained with rabbit anti-*H. pylori* polyclonal antibody (Dako Corp., Carpinteria, CA, USA) to detect *H. pylori*. Subtypes of intestinal metaplasia were assessed according to Filipe's criteria.⁸ Briefly, type I is characterized by mature goblet cells secreting acid sialomucins and sometimes sulfomucins, nonsecreting absorptive cells, and a well-defined brush border. Paneth cells are often present at the crypt base. Type II shows a mild architectural distortion, few or absent absorptive cells, and columnar cells containing a mixture of neutral and acid sialomucins; while goblet cells secrete sialomucins and occasionally sulfomucins. Paneth cells are rare or absent. In type III, the metaplastic foveae are tortuous, the architecture is disorganized, and immature columnar cells are abundant. Columnar cells secrete sulfomucin, while goblet cells contain sialomucin and sulfomucins. Paneth cells are absent. Attachment of *H. pylori* to segments of intestinal metaplasia was determined under the provision of Genta et al.⁹

Subtypes of intestinal metaplasia from 100 patients were 23 type I, 65 type II, and 12 type III. *H. pylori* attached to intestinal metaplasia was found in 17 patients; 1 (12.5%) patient had gastric cancer, 4 (16.7%) patients had gastric ulcers, 5 (45.5%) patients had duodenal ulcers, and 7 (12.3%) patients had chronic gastritis. In all cases, *H. pylori* was detected to be only adherent to type II (Fig. 1). These organisms lying in the mucus layer overlying the metaplastic epithelium were also observed in the foveolar space replaced by intestinal metaplasia, apparently attached to the intermediate cell and sometimes attached within the mucus vacuole of goblet cells. *H. pylori* was never detected in the area of intestinal absorptive cells and sulfomucin-containing metaplastic cells.

DISCUSSION

Many investigators have believed that *H. pylori* is absent from areas with intestinal metaplasia.⁵⁻⁷ The organisms are seen in the distal esophagus of less than one-half of patients with Barrett's esophagus, areas of gastric mucous cell metaplasia of duodenum, and heterotopic gastric mucosa in Meckel's diverticula and rectum.^{6,10-12} Our results showing adherence of *H. pylori* to areas of intestinal metaplasia are opposed to those studies. We think that routine H&E staining

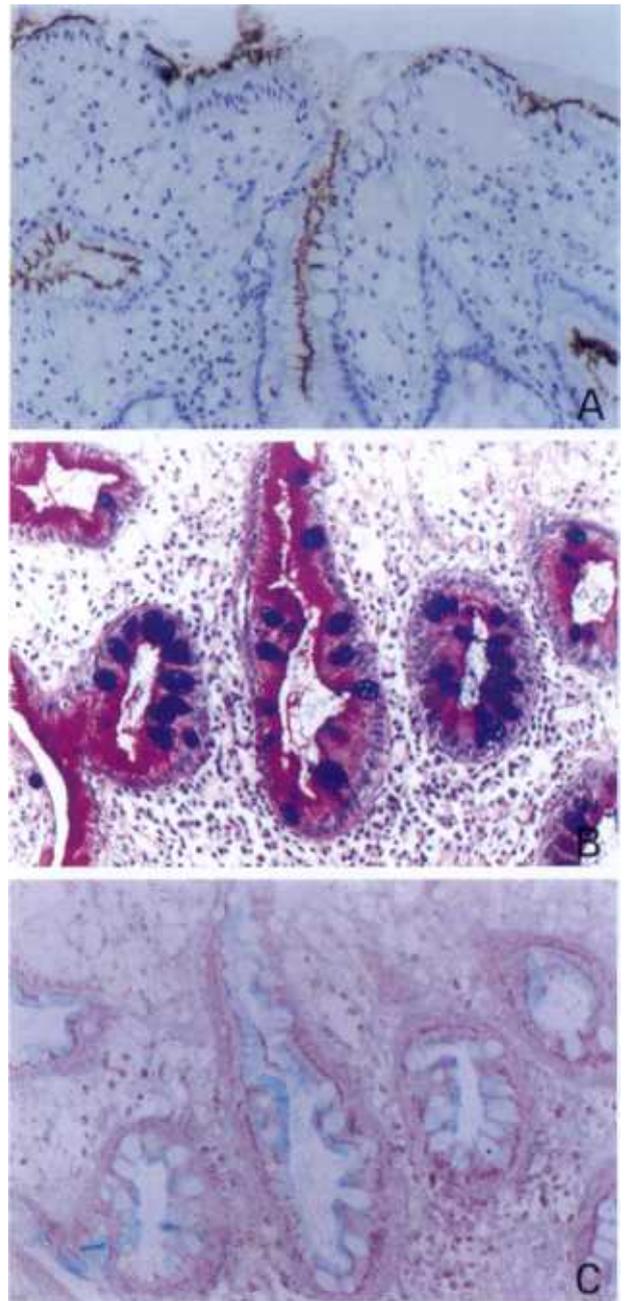


Fig. 1. Immunohistochemical stain of *H. pylori* (A) and histochemical mucin stain for intestinal metaplasia (B, C) in the same serial sections. Adherence of *H. pylori* to the areas of type II intestinal metaplasia, which consists of columnar cells secreting neutral mucin and sialomucin, and goblet cells secreting sialomucin (A, immunoperoxidase; B, periodic acid-Schiff/alcian blue pH 2.5; C, high-iron diamine/alcian blue pH 2.5, $\times 200$).

and the rarity of this occurrence may have led to a lack of recognition of adherence of *H. pylori* to areas of intestinal metaplasia. With H&E stain, *H. pylori*

are not well visualized and goblet cells are observed as empty circles. Thus, intimate association between bacteria and goblet cells may easily be overlooked. *H. pylori* are specifically observed with immunohistochemical stain, but it is difficult to observe details of mucosal morphology. Gastric mucosal morphology and *H. pylori* are easily observed by using immunohistochemistry associated with H&E stain. There are 3 reports in the literature of this organism colonizing areas of intestinal metaplasia in the antral mucosa. Steadman et al described the presence of *H. pylori* in areas of intestinal metaplasia in the antral biopsy specimens of 3 Australian patients.¹³ They suggested that *H. pylori* may not be actually adherent to the metaplastic areas; rather the organisms could be carried to these areas by the flow of mucus. However, we do not agree with their assertion because in our cases, *H. pylori* was detected not only in the mucus but also in clumps attached to intermediate cells and goblet cells in gastric pits. Genta et al conducted a study to evaluate the frequency of *H. pylori* adherence to areas of intestinal metaplasia in different populations.⁹ In 32 patients out of 378 *H. pylori*-infected patients, *H. pylori* was found in intimate contact with intestinal metaplasia, and 75% of the cases of documented adherence were Korean patients. They found that only 2 cases out of several thousand gastric biopsy specimens from North American patients infected with *H. pylori* showed adherence of *H. pylori* to the metaplastic epithelium. Misra et al reported 2 cases that *H. pylori* were seen in the gastric pits with intestinal metaplastic changes in the antral biopsy specimens of Indian patients.¹⁴ In Korea, *H. pylori* infection begins in infancy, and the infection rate reaches 50% at 5 years of age and maintains 80–90% after 8 years of age, whereas in developed countries, the infection rate reaches 20% at 20 years of age and is less than 50% at 50 years of age.^{15,16} Disparity between infection rates may explain why the frequency of *H. pylori* adherence to areas of intestinal metaplasia differ in different populations.

The most significant aspect of this study is that *H. pylori* attaches only to areas of type II intestinal metaplasia. All areas of intestinal metaplasia showing *H. pylori* adherence contained sialomucin, but *H. pylori* was not detected in the area of intestinal absorptive cells and sulfomucin-containing metaplastic cells. The brush border may represent a cellular structure that prevents the adherence of *H. pylori*,⁹ and type III

intestinal metaplasia, compared with type I and II, was reported to be less appropriate for survival of *H. pylori*.⁷ Any intestinal metaplasia-adherent *H. pylori* in a large series of Korean patients with gastric adenocarcinoma and extensive areas of incomplete intestinal metaplasia were not found.⁹ Intestinal type gastric cancer is often associated with type III intestinal metaplasia.^{17,18} These results suggest that type III intestinal metaplasia (sulfomucin-containing intestinal metaplasia) may be inhospitable for *H. pylori*, which explains our observation that all areas of intestinal metaplasia showing adherence contained sialomucin. But Genta et al reported that *H. pylori* was observed only adherent to either type II or III.⁹ Recently, intestinal metaplastic cell with adherent *H. pylori* represented hybrid epithelium sharing characteristics of both gastric surface mucous cells and intestinal metaplastic cells.¹⁹ It is unclear whether the progression from type I to type II and III intestinal metaplasia occurs. Longitudinal studies and the development of adequate experimental models are needed to resolve the relation between the progression of intestinal metaplasia and the survival of *H. pylori*.

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