The Resolution of Helicobacter suis-associated Gastric Lesions after Eradication Therapy

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Abstract:
A reddish depressed lesion was found in the corpus of the stomach of a 56-year-old man. Gastric biopsy showed no findings of mucosa-associated lymphoid tissue lymphoma, including lympho-epithelial lesions. A urea breath test, stool antigen test and serum IgG antibody to Helicobacter pylori test were negative. Magnifying endoscopy using narrow-band-imaging showed no malignant structures. Gastric biopsy specimens were subjected to immunohistochemistry and a polymerase chain reaction, which identified Helicobacter suis infection. Triple therapy with esomeprazole, metronidazole, and amoxicillin was administered for 10 days. Three months later, endoscopy showed the significant improvement of the lesion. H. suis infection should be considered in chronic gastritis patients without H. pylori infection.

Key words: Helicobacter suis, immunohistochemistry, PCR

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Introduction
Helicobacter pylori infection has been associated with the development of several diseases of the stomach. Other Helicobacters than H. pylori have also been found to inhabit the human stomach and these bacteria are called “gastric non-H. pylori Helicobacter (NHPH)” (1, 2). Helicobacter suis, formerly named “Helicobacter heilmannii type 1”, is one of the gastric NHPHs (3). H. suis infection has been shown to be associated with nodular gastritis (4) and mucosa-associated lymphoid tissue (MALT) lymphoma (5) in Japan. At present, H. suis is difficult to diagnose because of its lower urease activity in comparison to H. pylori (6) and there are no established methods to detect antibodies to H. suis (1). H. suis and other gastric NHPHs are not easily cultivated and the susceptibility of these bacteria to antibiotics has not been studied. Thus, the optimal eradication therapy for H. suis infection has not been established.

We herein report the case of a patient with a MALT lymphoma-like gastric mucosal lesion that was observed by endoscopy using narrow-band-imaging (NBI). We diagnosed H. suis infection based on the immunohistochemistry and polymerase chain reaction (PCR) findings and the gastric lesion disappeared after the successful eradication of H. suis.

Case Report
A 56-year-old man received esophagastroduodenoscopy (EGD) for gastric cancer screening. He did not take any medicines regularly and had never kept animals, including cats, dogs, or pigs. EGD revealed a large reddish depressed lesion in the greater curvature of the middle to lower corpus of the stomach. A ¹³C-urea breath test was negative with a value of 1.3‰ (cutoff value: 2.5) and a stool Helicobacter pylori (H. pylori) antigen test (Testmate Rapid Pylori Antigen; Wakamoto Pharmaceutical, Tokyo, Japan) was also negative. The patient’s serum IgG antibody to H. pylori titer was <3 U/mL (cutoff 10 U/mL, E-plate; Eiken, Tokyo, Japan). He had not previously undergone H. pylori eradication

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therapy. He was referred to our hospital for further examination. The results of peripheral blood, blood biochemistry and tumor marker analyses were within normal limits (Table). EGD showed the same lesion in the stomach (Fig. 1a and b) without a malignant structure (capillary dilatation, interstitial edema, or expansion of the white zone) or MALT lymphoma (tree-like appearance or nonstructural areas) by magnifying endoscopy using NBI (Fig. 1c and d). Only mild mononuclear infiltration with glandular atrophy were observed in the biopsy specimens, lymphoepithelial lesions (LELs) and H. pylori were not found (Fig. 2a). Giemsa staining was performed but no spiral bacteria was identified. Gastric biopsy specimens were taken from the greater curvature of the antrum and the greater curvature of upper corpus (Fig. 2b). DNA was extracted from the gastric biopsy specimens and a gastric mucosa by immunohistochemistry (Fig. 2b). DNA was less depressed and less red in color (Fig. 3). Biopsy specimen analyses were performed but no spiral bacteria was identified. Nested-PCR using specific primers to H. pylori was extracted from the gastric biopsy specimens and a possible route of transmission in this patient. Finally, the patient was diagnosed with chronic gastritis with H. suis infection.

He received triple therapy of esomeprazole (20 mg, twice a day; bid), metronidazole (250 mg; bid), and amoxicillin (750 mg; bid) for 10 days. Three months after finishing the triple therapy, EGD showed that the gastric mucosal lesion was less depressed and less red in color (Fig. 3). Biopsy specimens were subjected to immunohistochemistry and a nested-PCR and were found to be negative for H. suis. Recurrence of depressed reddish lesions was not observed in the two years since eradication, and he currently remains healthy.

Table. Laboratory Data on Admission.

| Hematology | Biochemistry |
|------------|--------------|
| WBC 4.230 /μL | TP 7.6 g/dL |
| Hb 15.0 g/dL | Alb 4.9 g/dL |
| Ptl 19.9 /μL | AST 25 U/L |
| Tumor marker | ALT 27 U/L |
| CEA 1.7 ng/mL | ALP 238 U/L |
| CA19-9 7 U/mL | LDH 153 U/L |
| sIL-2R 203 U/mL | γ-GTP 14 U/L |
| Helicobacter pylori tests | T-bil 1.0 mg/dL |
| Urea breath test - (1.4%/h) | BUN 11 mg/dL |
| Stool H. pylori antigen test - | Cre 0.90 mg/dL |
| Serum IgG antibody - (<3 U/mL) | Na 142 mmol/L |
| Serum IgM antibody - (<3 U/mL) | K 4.5 mmol/L |
| CRP <0.02 mg/dL | Cl 103 mmol/L |

WBC: white blood cell, Hb: hemoglobin, Ptl: platelets, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, sIL-2R: soluble interleukin-2 receptor, TP: total protein, Alb: Albumin, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein

Discussion

Gastric NHPHs were originally named as “H. heilmannii” and “Gastrospirillum hominis”. The prevalence of gastric NHPH infection has been considered to be low in comparison to H. pylori infection, with the rate of less than 0.5% in adults (2). Among the gastric NHPHs, H. suis has the highest prevalence in Belgium and Germany (8) and a higher prevalence of H. suis was seen in China (6.9%) (9). In Japan, the prevalence of H. suis is not high as that in China (1). Since the first case was reported in 1994 (10), H. suis infection has only been observed in a small number of cases with MALT lymphoma or nodular gastritis (4, 5).

Although gastric NHPHs have been recognized as zoonotic, the mechanism of transmission has not been determined (1). Close contact with dogs, and pigs is considered to be a risk factor for the acquisition of the gastric NHPH infection (11, 12). Previous studies have also suggested that gastric NHPH infection would occur after the successful eradication of H. pylori infection (13, 14). However, the present patient did not have any history of close contact with pigs or dogs, and had not previously undergone H. pylori infection eradication therapy. A recent study showed that visible H. suis persisted for 48 hours in contaminated pork (15). Thus, the consumption of contaminated pork was a possible route of transmission in this patient.

At present, the diagnosis of H. suis infection is difficult. H. suis has lower urease activity and the diagnostic methods that detect urease activity, such as the 14C-UBT and urease tests, are less sensitive in the detection of H. suis than they are in the detection of H. pylori (6). It is also impossible to distinguish H. pylori and H. suis infection based on positive
The eradication of gastric NHPHs have been performed

Figure 1. (a, b) Endoscopy revealed a large reddish depressed lesion in the greater curvature of the middle to lower corpus of the stomach. (c, d) Narrow-band-imaging did not show malignant structures.

results in a test detecting urease activity. Furthermore, gastric NHPHs are very difficult to culture from the gastric mucosa. Thus, the diagnosis of gastric NHPH infection is generally made based on the detection of their characteristic morphology in gastric biopsy specimens. Indeed, in many previous cases, the diagnosis of gastric NHPH infection was made using Giemsa-stained specimens. A recent report showed that immunohistochemistry was useful when gastric NHPHs were not found in Giemsa-stained biopsy specimens (4). In the present case, NHPH was not identified by Giemsa staining; however, the presence of NHPH was demonstrated by immunohistochemistry and a PCR was useful for identifying the species of NHPH as *H. suis*. A PCR was also useful for evaluating the *H. suis* status after eradication therapy (7).

NHPH infection has been recognized to be restricted to the antrum in most cases (16). In previous Japanese adult cases, endoscopy of the NHPH-infected gastric mucosa revealed spotty redness, erosion, ulcers and nodular gastritis in the antrum while the corpus mucosa remained normal without mucosal atrophy (4, 5, 10, 17-19). A recent case study proposed that a white marbled appearance in the gastric angle and antrum is a potential characteristic finding of the NHPH-infected gastric mucosa (20). However, in the present case, we did not observe erosion or a white marbled appearance in the antrum. On the other hand, a reddish lesion had developed in the greater curvature of the middle to lower corpus. Based on the histological findings of the lesion, it was considered that endoscopy showed a focally atrophic gastric mucosa with severe intestinal metaplasia and focal vascular congestion. The magnifying NBI findings were also compatible with intestinal metaplasia. According to the updated Sydney System (21), mononuclear cell infiltration was mild in the antrum and moderate in the corpus. Mild neutrophil infiltration was only seen in the corpus. These results suggest that, in the present case, the mucosal inflammation in the corpus was enhanced in comparison to that in the antrum even though the patient was infected with *H. suis*.

The eradication of gastric NHPHs have been performed
using regimens that are used for *H. pylori* eradication. Most Japanese cases with gastric NHPH infection have been successfully eradicated with a triple therapy that included a proton pump inhibitor, amoxicillin and clarithromycin. In the present case, the duration of the eradication therapy was 10 days. In previous Japanese cases, the duration of treatment ranged from 7 to 14 days (4, 5, 17-20). As the eradication therapy for this patient was not covered by the health insurance system, the patient decided himself to receive 10-day treatment after he was informed that treatment duration [with proton pump inhibitor (PPI)-based triple therapy] of 7-10 or 10-14 days had been associated with significantly higher eradication rates in patients with *H. pylori* infection (22).

In summary, an *H. suis* infection should be considered when chronic gastritis with a specific endoscopic appearance is observed in patients who were not infected with *H. pylori*, even when the lesions develop in the corpus. Immunohistochemistry and a PCR are useful for the diagnosis of gastric NHPH.

The authors state that they have no Conflict of Interest (COI).

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