

[ CASE REPORT ]

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

Satoru Nakagawa<sup>1</sup>, Tadashi Shimoyama<sup>1</sup>, Masahiko Nakamura<sup>2</sup>, Daisuke Chiba<sup>1</sup>,  
Hidezumi Kikuchi<sup>1</sup>, Manabu Sawaya<sup>1</sup>, Daisuke Chinda<sup>1</sup>,  
Tatsuya Mikami<sup>1</sup> and Shinsaku Fukuda<sup>1</sup>

### 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 esophagogastroduodenoscopy (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 middle to lower corpus of the stomach. A <sup>13</sup>C-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

<sup>1</sup>Department of Gastroenterology, Hirosaki University Graduate School of Medicine, Japan and <sup>2</sup>Division of Pathophysiology, Research and Education Center for Clinical Pharmacy, School of Pharmaceutical Sciences, Kitasato University, Japan

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Correspondence to Dr. Tadashi Shimoyama, tsimo-hki@umin.ac.jp

**Table. Laboratory Data on Admission.**

Hematology		Biochemistry	
WBC	4,230 / $\mu$ L	TP	7.6 g/dL
Hb	15.0 g/dL	Alb	4.9 g/dL
Plt	19.9 / $\mu$ L	AST	25 U/L
		ALT	27 U/L
		ALP	238 U/L
Tumor marker		LDH	153 U/L
CEA	1.7 ng/mL	$\gamma$ -GTP	14 U/L
CA19-9	7 U/mL	T-bil	1.0 mg/dL
sIL-2R	203 U/mL	BUN	11 mg/dL
		Cre	0.90 mg/dL
<i>Helicobacter pylori</i> tests		Na	142 mmol/L
Urea breath test	- (1.4‰)	K	4.5 mmol/L
Stool <i>H. pylori</i> antigen test	-	Cl	103 mmol/L
Serum IgG antibody	- (<3 U/mL)	CRP	<0.02 mg/dL

WBC: white blood cell, Hb: hemoglobin, Plt: platelets, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, sIL2-R: 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,  $\gamma$ -GTP:  $\gamma$ -glutamyl transpeptidase, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein

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 to detect infection with *Helicobacter* spp. other than *H. pylori*. Anti-*Helicobacter* spp. antibodies were detected in the gastric mucosa by immunohistochemistry (Fig. 2b). DNA was extracted from the gastric biopsy specimens and a nested-PCR using specific primers to *H. suis* (7) was positive (Fig. 2c). Finally, the patient was diagnosed with chronic gastritis with *H. suis* infection.

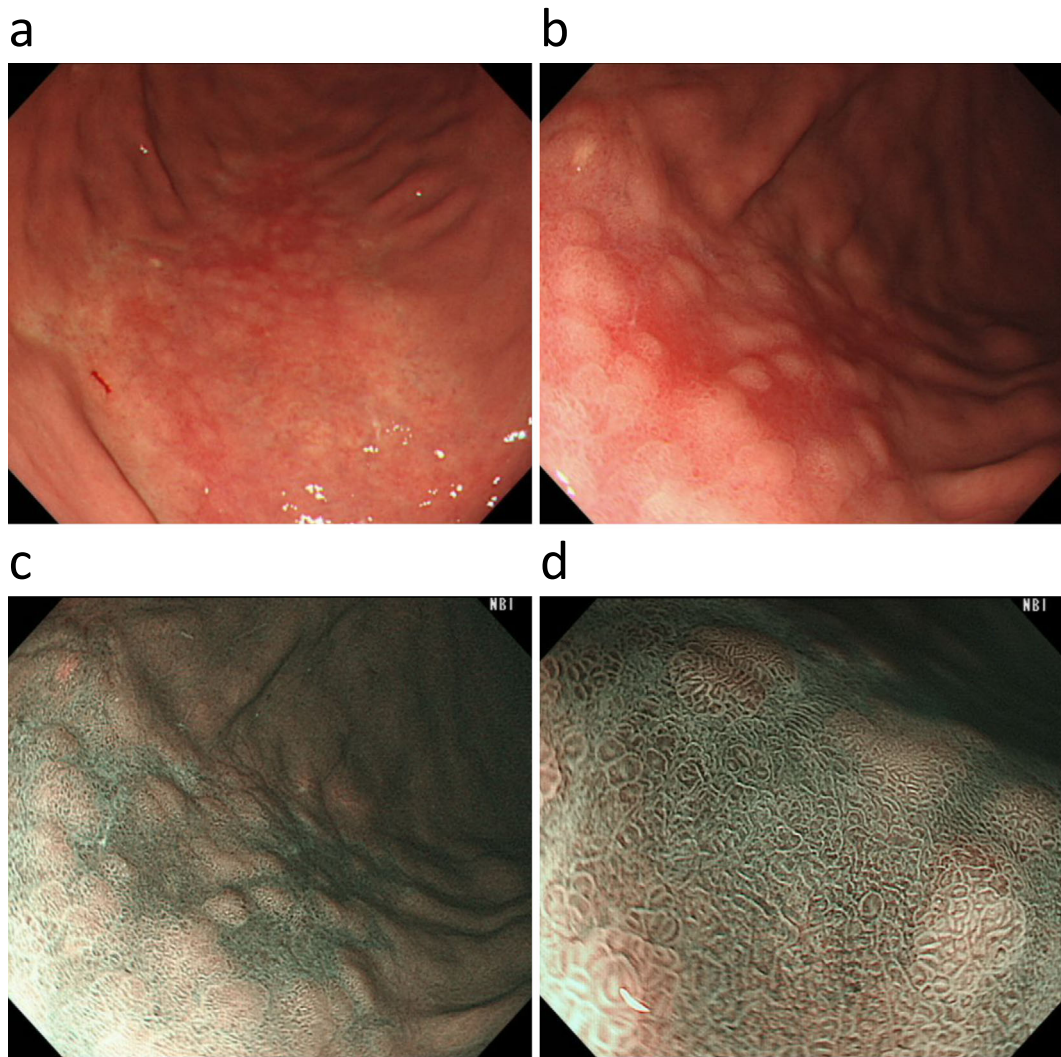
He received triple therapy of esomeprazole (20 mg, twice a day; bid), metronidazole (250 mg; bid), and amoxicillin (750 mg; bid) for 10 days. Three months after finishing the triple therapy, EGD showed that the gastric mucosal lesion was less depressed and less red in color (Fig. 3). Biopsy specimens 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.

## 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 viable *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  $^{13}$ C-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



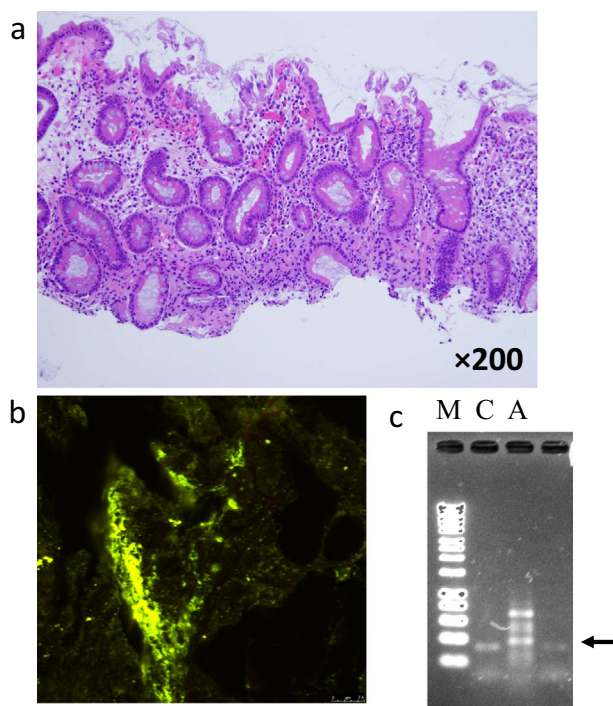
**Figure 1.** (a, b) Endoscopy revealed a large reddish depressed lesion in the greater curvature of the middle to lower corpus of the stomach. (c, d) Narrow-band-imaging did not show malignant structures.

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 with-

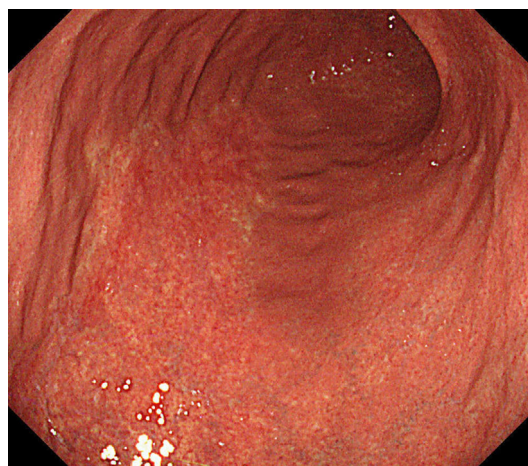
out mucosal atrophy (4, 5, 10, 17-19). A recent case study proposed that a white marbled appearance in the gastric angle and antrum is a potential characteristic finding of the NHPH-infected gastric mucosa (20). However, in the present case, we did not observe erosion or a white marbled appearance in 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



**Figure 2.** (a) The microscopic findings of a specimen from the lesion showing mononuclear cell infiltration and glandular atrophy with intestinal metaplasia. Focal small vascular congestion was also observed in the mucosa. Neither centrocyte-like (CCL) cells nor lymphoepithelial lesions (LELs) were observed (Hematoxylin and Eosin staining). (b) Immunohistochemistry of a gastric biopsy specimen using anti-*Helicobacter* spp. antibodies. Green spots indicate the presence of *Helicobacter* spp. (c) The results of a nested-polymerase chain reaction (PCR) using specific primers to *H. suis*. PCR products of the expected size were observed. M: molecular weight marker, A: antral mucosa, C: corpus mucosa

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 (4, 5, 17, 20). In the present case, we used metronidazole because clarithromycin had previously been used to treat an upper respiratory infection. As described, gastric NHPHs are difficult to cultivate from gastric biopsy specimens and there are no data on the susceptibility NHPHs isolated from humans to antibiotics. Our results might suggest that metronidazole is effective for the treatment of *H. suis* infection when clarithromycin-containing therapy is not successful. 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. py-*



**Figure 3.** Gastrointestinal endoscopy revealed the improvement of the gastric lesion after the eradication of *Helicobacter suis*.

*lori* 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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