

## Two Cases of Chronic Gastritis with *non-Helicobacter pylori Helicobacter* Infection

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### Abstract

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Two men, 48 and 54 years of age, were referred for medical checkups without any particular symptoms. Upper gastrointestinal endoscopy showed a normal gastric body, but white marbled appearance in the lesser curvature of the gastric angle and antrum. Biopsy specimens revealed relatively long and tightly coiled organisms. The two patients were diagnosed as having *non-Helicobacter pylori helicobacter* (NHPH) infection according to the findings of pathological and quantitative reverse transcription-polymerase chain reaction (qRT-PCR) analyses. After triple therapy (amoxicillin, clarithromycin, and rabeprazole), endoscopy showed an improvement of the white marbled lesions and biopsy specimens showed no NHPH. The white marbled appearance limited to the gastric angle and antrum may be a potential characteristic finding of NHPH-infected gastritis.

**Key words:** *Helicobacter* species, *Helicobacter pylori*, *Helicobacter suis*, *non-Helicobacter pylori helicobacter*, chronic gastritis

(Intern Med 55: 1865-1869, 2016)

(DOI: 10.2169/internalmedicine.55.5891)

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### Introduction

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*Helicobacter pylori* (*H. pylori*) infection is specific to the human stomach and has been shown to be associated with chronic gastritis, gastroduodenal ulcers, gastric mucosa associated lymphoid tissue (MALT) lymphoma, and gastric cancer. In addition to *H. pylori*, tightly coiled and relative long bacteria, called *non-H. pylori helicobacter* (NHPH), have been observed in the human stomach. NHPH species naturally colonize the stomach of domestic animals including pigs, dogs and cats. NHPH has been shown to be associated with chronic gastritis, peptic ulcers and MALT lymphoma, however, the characteristics of NHPH infection have not been clarified because endoscopic characteristic findings of

NHPH-infected gastritis are unknown and the differential diagnosis from *H. pylori* is difficult. The latest improvement in quantitative reverse transcription-polymerase chain reaction (qRT-PCR) has made it possible to accurately diagnose NHPH infections, including infections with *H. suis* and *H. heilmannii*. In this report, two cases of NHPH infection including endoscopic findings of the stomach are described.

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### Case Reports

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#### Case 1

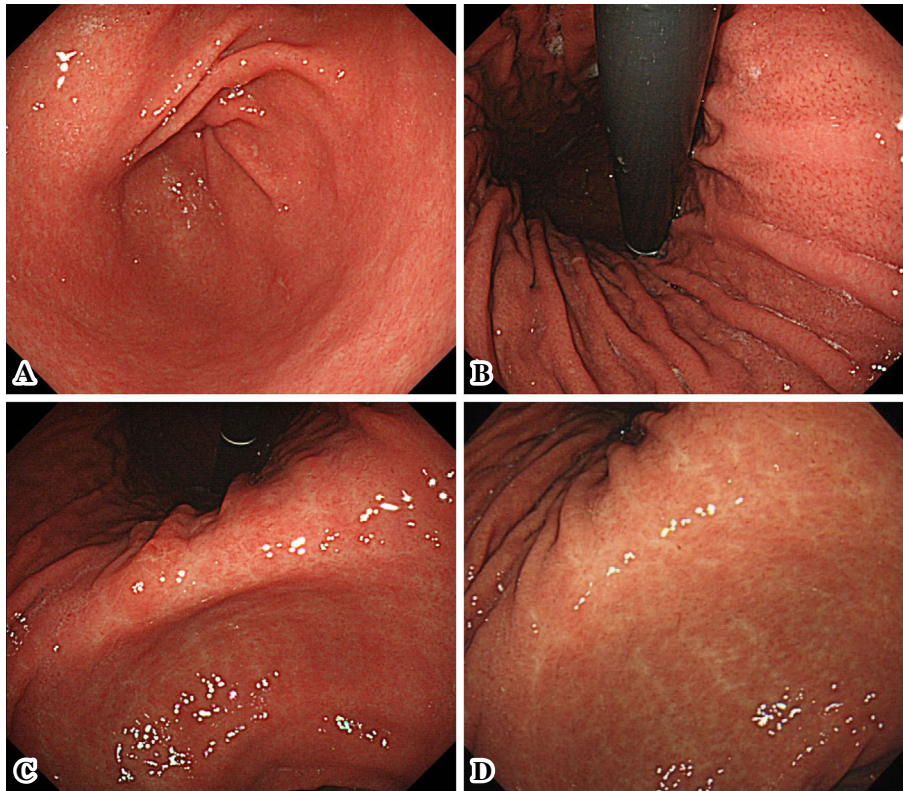
A 48-year-old man was referred for a medical checkup without any particular symptoms. He had a medical history of a gallstone and dyslipidemia and had not taken any medi-

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Received for publication June 2, 2015; Accepted for publication October 25, 2015

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**Figure 1.** (A) Upper gastrointestinal endoscopy showed a normal antrum. (B) RAC was shown in the lower part of the gastric body. (C) Slight marbled erosions were observed in the lesser curvature of the gastric angle. RAC: regular arrangement of collecting venules. (D) The white marbled appearance improved 6 months after eradication therapy.

cine. Esophagogastroduodenoscopy showed a nearly normal antrum (Fig. 1A) and regular arrangement of collecting venules (RAC) (1) in the lower part of the gastric body (Fig. 1B), suggesting *H. pylori*-uninfected mucosa. However, a white marbled appearance was observed in the lesser curvature of the gastric angle (Fig. 1C). The result of a urea breath test (UBT: UBiT, Otsuka Pharmaceutical, Tokyo, Japan) was 2.5‰ (cut-off value: 2.5‰), a *H. pylori* stool antigen test (Premier Platinum HpSA PLUS/Meridian HpSA ELISA II, Meridian Bioscience, Cincinnati, USA) was negative, and a rapid urease test (RUT: Pylori Tek, Eidia, Tokyo, Japan) was weakly positive. Biopsy specimens were taken from the greater curvature of the antrum, gastric body and the lesser curvature of the gastric angle. Biopsy specimens of the lesser curvature of the gastric angle revealed neutrophil infiltration by hematoxylin and eosin staining (Fig. 2A) and relatively long and wide organisms by Giemsa staining (Fig. 2B), suggesting NHPH infection. Long spiral-shaped organisms were observed in indirect immunofluorescence of *H. pylori* (Fig. 2C, D). We obtained informed consent from this patient and performed PCR (2). *H. pylori*-specific PCR was negative and PCR for detecting NHPH was positive, however, the species of the organism was not identified due to a limited amount of available DNA. After one-week triple therapy with amoxicillin, clarithromycin, and rabeprazole, the UBT had decreased to 0.5‰. Esophagogastroduodenoscopy was performed six months after eradication therapy,

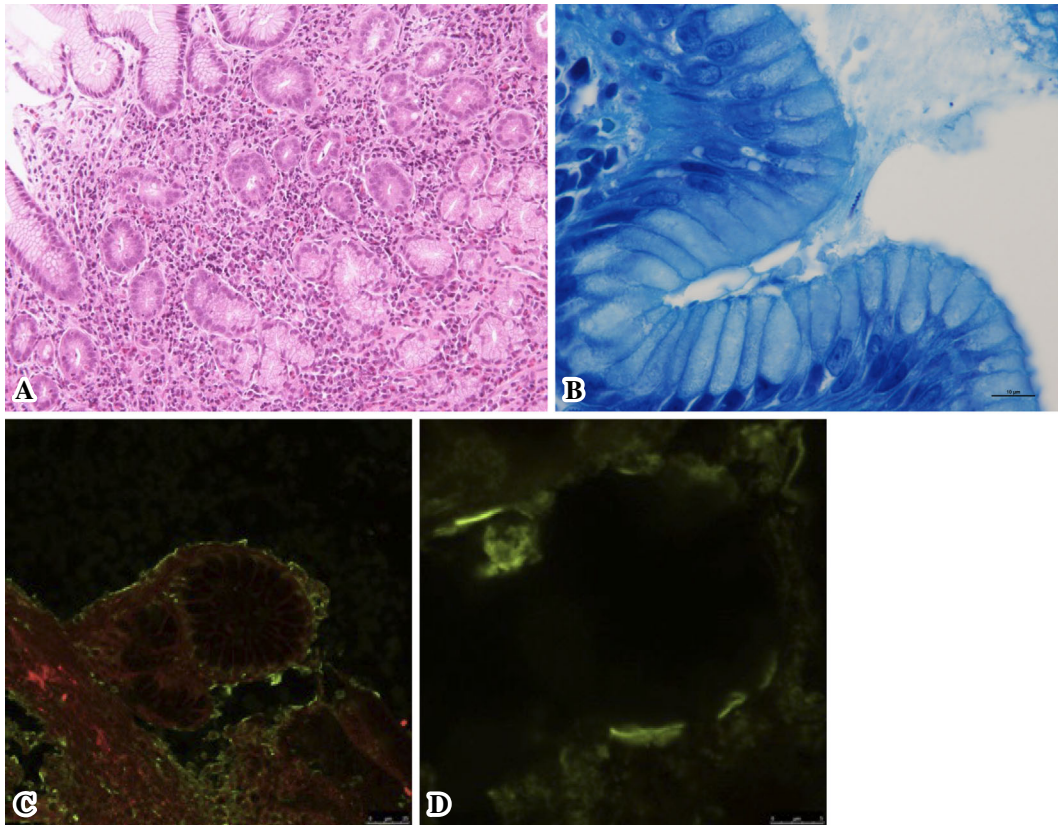
which showed an improvement of the white marbled appearance (Fig. 1D), and the biopsy specimens showed no neutrophil infiltration or NHPH.

## Case 2

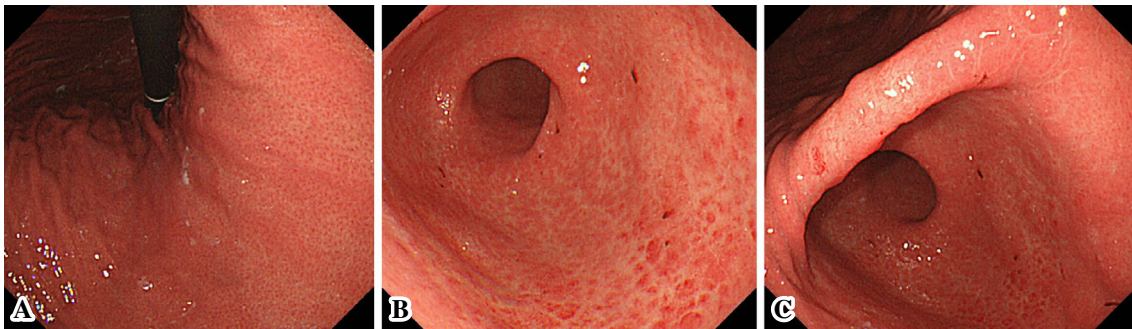
A 54-year-old man was referred for a medical checkup without any symptoms. Esophagogastroduodenoscopy showed RAC in the lower part of the gastric body (Fig. 3A), but spotty redness in the antrum (Fig. 3B) and a white marbled appearance in the lesser curvature of the gastric angle (Fig. 3C). Biopsy specimens were taken from similar areas to Case 1, which revealed infiltration of various inflammatory cells in the antrum (Fig. 4A) and the same findings as those in Case 1 in the lesser curvature of the gastric angle (Fig. 4B, C). *H. pylori*-specific PCR was negative and PCR for detecting NHPH was positive; subsequent *H. suis*-specific PCR was positive.

## Discussion

In both cases, esophagogastroduodenoscopy showed RAC in the lower part of the gastric body, which is a diagnostic feature of *H. pylori*-uninfected mucosa (1), but a white marbled appearance in the lesser curvature of the gastric angle and antrum. Some case studies showed erosions and ulcers in the antrum and pyloric ring in NHPH-infected gastritis (3-5). As endoscopic findings in the gastric body, mildly



**Figure 2.** Biopsy specimens of the lesser curvature of the gastric angle. (A) Infiltration of neutrophils was shown by Hematoxylin and Eosin staining (original magnification 100 $\times$ ). (B) Relatively long and wide organisms were observed by Giemsa staining (original magnification 1,000 $\times$ ). (C, D) Long spiral-shaped organisms were observed by indirect immunofluorescence of *H. pylori* (C: original magnification 200 $\times$ ; D: original magnification 1,000 $\times$ ).



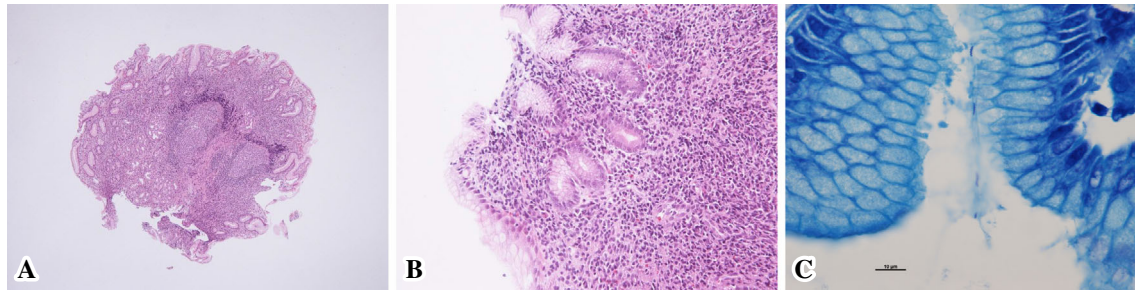
**Figure 3.** (A) Upper gastrointestinal endoscopy showed RAC in the lower part of the gastric body. (B) Redness and a coarse appearance were observed in the antrum. (C) Slight marbled erosions were observed in the lesser curvature of the gastric angle. RAC: regular arrangement of collecting venules

erythematous and micronodular mucosa were shown in one case (3), while there was no atrophy in another case (5).

In humans, infection with NHPH has been shown to be associated with gastritis, gastric ulceration, and gastric MALT lymphoma (6-9). NHPH-infected animals suffer from nodular gastritis (10) and MALT lymphoma (11). NHPH is divided into *H. heilmannii* type 1 (*H. suis*) and *H. heilmannii* type 2 (*H. felis*, *H. bizzozeronii*, *H. salmonis* and *H. heilmannii*) according to a sequence analysis of the 16S RNA genes (12). The rate of NHPH infection is reported to be

0.2-6% (6, 7, 13-15), and the most prevalent NHPH species in humans is *H. suis* (16). However, the details of NHPH infection have not been clarified due to the absence of endoscopic characteristic findings of NHPH-infected gastritis and the difficulty in a precise differential diagnosis from *H. pylori*.

Serum anti-*H. pylori* antibody and *H. pylori* stool antigen are negative in NHPH infection, however, RUT and UBT are occasionally weakly positive because of the lower activity of NHPH urease (5, 6). NHPH is observed as more



**Figure 4.** (A) Biopsy specimens revealed infiltration of various inflammatory cells in the antrum (original magnification 40×). (B) Infiltration of neutrophils in the lesser curvature of the gastric angle was shown by Hematoxylin and Eosin staining (original magnification 200×). (C) Relatively long and wide organisms were observed in the lesser curvature of the gastric angle by Giemsa staining (original magnification 1,000×).

tightly coiled and longer bacteria than *H. pylori*. Case 1 was consistent with NHPH infection in that *H. pylori* stool antigen was negative, rapid urease test and urease breath test were weakly positive, and large bacteria were observed in the biopsy specimens. Moreover, NHPH infection was definitively diagnosed in both cases by advanced quantitative real-time PCR-PCR (qRT-PCR).

NHPH can be transmitted to humans from animals such as pigs and pets because NHPH is a zoonosis unlike *H. pylori*. However, neither of our patients had regular contact with pigs or any pets.

Combination therapies with a proton pump inhibitor, amoxicillin, and clarithromycin or metronidazole as well as *H. pylori* treatment have been shown to be effective for NHPH in some cases (4, 5, 17). Eradication of NHPH by one-week triple therapy was successful in Case 1. Both the endoscopic finding of a white marbled appearance and histological findings of activity and inflammation were improved after successful eradication.

In this case report, two cases of chronic gastritis with NHPH infection were described. The white marbled appearance in the lesser curvature of the gastric angle and antrum is a potential characteristic finding of NHPH-infected gastritis. Reports of NHPH infection remain rare, thus a greater accumulation of NHPH infection cases is necessary.

#### Author's disclosure of potential Conflicts of Interest (COI).

Satoka Shiratori: Employment, SAPPORO MEDICAL CENTER NTT EC. Katsuhiko Mabe: Honoraria, Takeda Pharmaceutical and Eisai; Research funding, Eisai. Shinji Yoshii: Employment, SAPPORO MEDICAL CENTER NTT EC. Yasunari Takakuwa: Employment, SAPPORO MEDICAL CENTER NTT EC. Masaaki Sato: Employment, SAPPORO MEDICAL CENTER NTT EC. Mototsugu Kato: Honoraria, Eisai, Daiichi Sankyo and AstraZeneca; Research Funding, Eisai, Takeda Pharmaceutical, Daiichi Sankyo, AstraZeneca and Astellas Pharma. Masahiro Asaka : Research funding, Takeda Pharmaceutical and Eisai. Naoya Sakamoto: Honoraria, Bristol-Myers Squibb and Janssen Pharmaceutical; Research funding, Chugai Pharmaceutical and Bristol-Myers Squibb.

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