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## Observational Study

# Clinical features of cardiac nodularity-like appearance induced by *Helicobacter pylori* infection

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### Institutional review board

**statement:** This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 6, 2019 (approval no. S1909-U06).

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Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were

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## Abstract

### BACKGROUND

We have previously reported that *Helicobacter pylori* (*H. pylori*)-associated nodular gastritis could occur in both the antrum and the cardia. Cardiac nodularity-like appearance (hereafter, called as cardiac nodularity) had a high predictive accuracy for the diagnosis of *H. pylori* infection. In the previous study, we included only the patients who were evaluated for *H. pylori* infection for the first time, and excluded patients with a history of eradication. Therefore, the prevalence and clinical features of cardiac nodularity remains unknown.

### AIM

To perform this cross-sectional study to explore the characteristics of cardiac nodularity.

### METHODS

Consecutive patients who underwent esophagogastroduodenoscopy between



obtained after each patient agreed to treatment by written consent.

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There are no conflicts of interest to report.

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No additional data are available.

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May, 2017 and August, 2019 in the Toyoshima Endoscopy Clinic were enrolled in this study. We included *H. pylori*-negative, *H. pylori*-positive, and *H. pylori*-eradicated patients, and excluded patients with unclear *H. pylori* status and eradication failure. *H. pylori* infection was diagnosed according to serum anti-*H. pylori* antibody and the urea breath test or histology. Cardiac nodularity was defined as a miliary nodular appearance or the presence of scattered whitish circular small colorations within 2 cm of the esophagogastric junction. Nodularity was visualized as whitish in the narrow-band imaging mode. We collected data on the patients' baseline characteristics.

## RESULTS

A total of 1078 patients were finally included. Among *H. pylori*-negative patients, cardiac nodularity and antral nodularity were recognized in 0.14% each. Among *H. pylori*-positive patients, cardiac nodularity and antral nodularity were recognized in 54.5% and 29.5%, respectively. Among *H. pylori*-eradicated patients, cardiac nodularity and antral nodularity were recognized in 4.5% and 0.6%, respectively. The frequency of cardiac nodularity was significantly higher than that of antral nodularity in *H. pylori*-positive and -eradicated patients. The frequencies of cardiac nodularity and antral nodularity in *H. pylori*-eradicated patients were significantly lower than those in *H. pylori*-positive patients ( $P < 0.001$ ). The patients with cardiac nodularity were significantly younger than those without cardiac nodularity ( $P = 0.0013$ ). Intestinal metaplasia score of the patients with cardiac nodularity were significantly lower than those without cardiac nodularity ( $P = 0.0216$ ). Among *H. pylori*-eradicated patients, the patients with cardiac nodularity underwent eradication significantly more recently compared with those without cardiac nodularity ( $P < 0.0001$ ).

## CONCLUSION

This report outlines the prevalence and clinical features of cardiac nodularity, and confirm its close association with active *H. pylori* infection.

**Key Words:** Cardia; Nodularity; *Helicobacter pylori*; Diagnosis; Gastritis

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**Core Tip:** The prevalence of cardiac and antral nodularity in *Helicobacter pylori* (*H. pylori*) -negative, -positive, and -eradicated patients were 0.14% and 0.14%, 54.5% and 29.5%, and 4.5% and 0.6%, respectively. Cardiac nodularity was more frequent than antral nodularity in *H. pylori*-positive and -eradicated patients. Cardiac nodularity was often found in younger patients and patients with less intestinal metaplasia. Cardiac nodularity decreased after eradication, especially in patients who underwent eradication a long time ago.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection leads to the development of gastric atrophy, peptic ulcer, and gastric cancer<sup>[1-5]</sup>. Eradication of *H. pylori* infection has been reported as an effective strategy for treating atrophic gastritis and peptic ulcer, and preventing gastric cancer<sup>[6-9]</sup>. Therefore, it is important to evaluate *H. pylori* infection status<sup>[10-12]</sup>.

Nodular gastritis is a form of chronic gastritis that has a unique miliary pattern on endoscopy, with "gooseflesh-like" appearance. Many studies have shown a strong association between nodular gastritis and *H. pylori* infection<sup>[13-15]</sup>. Children and young women are reported to be predisposed to nodular gastritis. Nodular gastritis improves

gradually with age<sup>[16]</sup>. Several reports have suggested an association between nodular gastritis and diffuse type gastric cancer<sup>[13,15,17]</sup>.

We have previously reported that nodularity could occur in both the antrum and the cardia<sup>[18]</sup>. Cardiac nodularity-like appearance is found more frequently than antral nodularity. Cardiac nodularity-like appearance (hereafter, called as cardiac nodularity) had a high predictive accuracy for the diagnosis of *H. pylori* infection. Our previous report also showed excellent interobserver agreement on cardiac nodularity. Furthermore, histological examination of cardiac nodularity often revealed lymphoid follicles displaying lymphocyte infiltration in the cardiac gland<sup>[18]</sup>.

However, the prevalence and clinical features of cardiac nodularity remains unknown. Therefore, we performed this cross-sectional study to explore the characteristics of cardiac nodularity.

## MATERIALS AND METHODS

### Ethics

This study was approved by the ethical review committee of Hattori Clinic on September 6, 2019 (approval no. S1909-U06)<sup>[12,19]</sup>. All clinical investigations were conducted according to the ethical guidelines of the Declaration of Helsinki.

### Patients

Consecutive patients who underwent esophagogastroduodenoscopy (EGD) between May, 2017 and August, 2019 in the Toyoshima Endoscopy Clinic were enrolled in this study. Inclusion criteria included defined *H. pylori* status (*H. pylori*-negative patients, *H. pylori*-positive patients, and *H. pylori*-eradicated patients). The patients with unclear *H. pylori* status and eradication failure were excluded from the study. EGD was conducted for the examination of symptoms and screening. We collected data on the patients' baseline characteristics, including age and sex, and period since eradication for eradicated patients.

### Endoscopic procedures

EGD was performed using the Olympus Evis Lucera Elite system with a GIF-H290Z or GIF-HQ290 endoscope (Olympus Corporation, Tokyo, Japan)<sup>[20]</sup>. An expert physician (Toyoshima O) performed endoscopic procedures. Furthermore, EGD images were retrospectively reviewed by other expert physicians. Discrepancies in diagnosis between the two sets of physicians were resolved through discussion. Sedation with midazolam and/or pethidine was performed at the patient's discretion<sup>[21-23]</sup>. Antral nodularity was defined as a miliary nodular appearance consisting of whitish circular micronodules measuring  $\leq 1$  mm in both height and diameter. Cardiac nodularity was defined as a miliary nodular appearance or the presence of scattered whitish circular small colorations within 2 cm of the esophagogastric junction. Nodularity was visualized as whitish in the narrow-band imaging (NBI) mode. The representative endoscopic images are shown in Figure 1.

We scored atrophy, intestinal metaplasia, diffuse redness, and enlarged folds, according to the Kyoto classification<sup>[24]</sup>.

Endoscopic atrophy was diagnosed based on the Kimura and Takemoto classification<sup>[25]</sup>. Non-atrophy and C1 were scored as Atrophy score 0, C2, and C3 as Atrophy score 1, and O1 to O3 as Atrophy score 2.

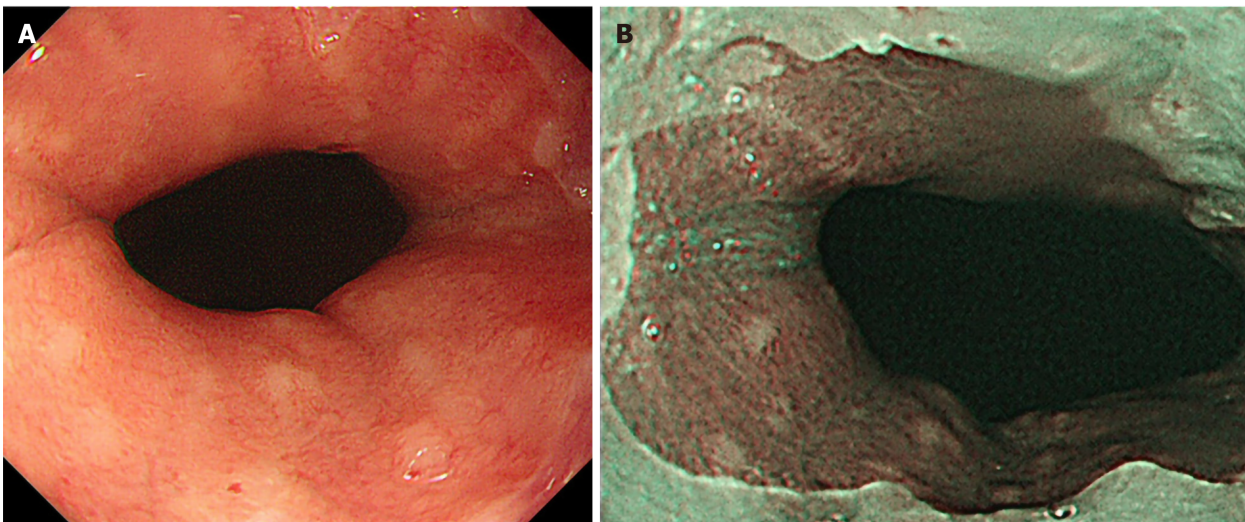
The absence of intestinal metaplasia was scored as Intestinal metaplasia score 0, the presence of intestinal metaplasia within the antrum as Intestinal metaplasia score 1, and intestinal metaplasia extending into the corpus as Intestinal metaplasia score 2. The Intestinal metaplasia score was diagnosed using white light imaging.

The absence of diffuse redness was scored as Diffuse redness score 0, mild diffuse redness or diffuse redness with regular arrangement of collecting venules (RAC) as Diffuse redness score 1, and severe diffuse redness or diffuse redness without RAC as Diffuse redness score 2.

The absence and presence of enlarged folds was scored as Enlarged folds score 0 and 1, respectively.

### Diagnosis of *H. pylori* infection

Serum anti-*H. pylori* antibody was measured on the day of EGD. The antibody titer was measured using an enzyme immunoassay kit with antigens derived from Japanese individuals (E-plate Eiken *H. pylori* antibody II; Eiken Chemical, Tokyo,



**Figure 1 Endoscopic images of cardiac nodularity-like appearance.** A: White light observation. A miliary pattern with a “gooseflesh-like” appearance was found in the cardia. Whitish circular micronodules measuring  $\leq 1$  mm in both diameter and height were observed; B: Narrow-band imaging observation. Whitish coloration denoted nodularity.

Japan). An antibody titer  $\geq 10$  U/mL (the cut-off value recommended by the manufacturer) was considered positive for *H. pylori*<sup>[26]</sup>. When the serum anti-*H. pylori* antibody titer was 3.0-9.9 U/mL, the findings of urea breath test or histological assessment was added. If either the urea breath test or histology was positive, patients were considered positive for *H. pylori*<sup>[27,28]</sup>. An antibody titer  $< 3.0$  U/mL or negative urea breath test was considered to indicate *H. pylori* negativity. Eradication was confirmed by urea breath test.

### Statistical analysis

Categorical data were compared using the chi-square test. Continuous data were compared using Student's or Welch's *t*-test, as appropriate. A two-sided *P* value of  $< 0.05$  was considered as statistically significant. Calculations were carried out by the Stat Mate IV software (ATOMS, Tokyo, Japan).

## RESULTS

The endoscopist performed 1215 EGDs during the study period. We excluded 137 patients (135 patients with unclear *H. pylori* infection status and two with eradication failure). A total of 1078 patients were finally included.

The characteristics of the participants in the present study are shown in Table 1. Among *H. pylori*-negative patients, cardiac nodularity and antral nodularity were recognized in one patient each (0.14% each). Among *H. pylori*-positive patients, cardiac nodularity and antral nodularity were recognized in 24 (54.5%) and 13 (29.5%) patients, respectively. The frequency of cardiac nodularity was significantly higher than that of antral nodularity ( $P < 0.05$ ). Among *H. pylori*-eradicated patients, cardiac nodularity and antral nodularity were recognized in 15 (4.5%) and 2 (0.6%) patients, respectively. The frequency of cardiac nodularity was significantly higher than that of antral nodularity ( $P < 0.01$ ). The frequencies of cardiac nodularity and antral nodularity in *H. pylori*-eradicated patients were significantly lower than those in *H. pylori*-positive patients ( $P < 0.001$ ).

Clinical characteristics of cardiac nodularity in *H. pylori*-positive patients are shown in Table 2. The patients with cardiac nodularity were significantly younger than those without cardiac nodularity ( $P = 0.0013$ ). Intestinal metaplasia score of the patients with cardiac nodularity were significantly lower than those without cardiac nodularity ( $P = 0.0216$ ).

Among *H. pylori*-eradicated patients, the patients with cardiac nodularity were also significantly younger than those without cardiac nodularity ( $P = 0.0003$ , Table 3). Furthermore, the patients with cardiac nodularity underwent eradication significantly more recently compared with those without cardiac nodularity ( $P < 0.0001$ ).



**Table 1 Characteristics of enrolled subjects**

	<i>H. pylori</i> negative	<i>H. pylori</i> positive	<i>H. pylori</i> eradicated
Patient number	704	44	330
Mean age (standard deviation)	54.2 ± 11.1	51.0 ± 13.4	60.3 ± 12.3
Male:female	358:346	19:25	185:145
Cardiac nodularity	1 (0.14%)	24 (54.5%) <sup>a</sup>	15 (4.5%) <sup>bf</sup>
Antral nodularity	1 (0.14%)	13 (29.5%)	2 (0.6%) <sup>f</sup>

<sup>a</sup>*P* < 0.05,<sup>b</sup>*P* < 0.01 *vs* antral nodularity;<sup>f</sup>*P* < 0.001 *vs* *Helicobacter pylori* positive. *H. pylori*: *Helicobacter pylori*.**Table 2 Clinical characteristics of cardiac nodularity in *Helicobacter pylori* positive patients**

	Cardiac nodularity (+)	Cardiac nodularity (-)	<i>P</i> value
Patient number	24	20	
Mean age (standard deviation)	44.9 ± 7.8	58.3 ± 15.1	0.0013
Male:female	9:15	10:10	0.598
Atrophy score	1.46 ± 0.59	1.55 ± 0.51	0.588
Intestinal metaplasia score	0.21 ± 0.59	0.80 ± 0.95	0.0216
Enlarged fold score	0.54 ± 0.51	0.60 ± 0.50	0.705
Diffuse redness score	1.75 ± 0.55	1.67 ± 0.64	0.648

**Table 3 Clinical characteristics of cardiac nodularity in *Helicobacter pylori* eradicated patients**

	Cardiac nodularity (+)	Cardiac nodularity (-)	<i>P</i> value
Patient number	15	315	
Mean age (standard deviation)	49.2 ± 12.3	60.8 ± 12.1	0.0003
Male:female	5:10	180:135	0.121
Months after eradication	41.5 ± 30.1	91.6 ± 100.0	< 0.0001

## DISCUSSION

The prevalence of cardiac nodularity was 0.14%, 54.5%, and 4.5% in *H. pylori*-negative, -positive, and -eradicated patients, respectively. Cardiac nodularity was more frequent than antral nodularity in *H. pylori*-positive and -eradicated patients. Cardiac nodularity was often found in younger patients and patients with less intestinal metaplasia. Cardiac nodularity decreased after eradication, especially in patients who underwent eradication a long time ago.

Our previous study showed excellent prediction accuracy of cardiac nodularity due to *H. pylori* infection, with 0.928 of accuracy, 0.996 of specificity, 0.571 of sensitivity, 0.960 of positive predictive value, and 0.925 of negative predictive value<sup>[18]</sup>. In our previous study, we included only the patients who were evaluated for *H. pylori* infection for the first time, and excluded patients with a history of eradication. However, the present cross-sectional study included the patients with a history of eradication also. The frequency of cardiac nodularity in *H. pylori*-positive patients was remarkably higher than that in *H. pylori*-negative patients and *H. pylori*-eradicated patients. Cardiac nodularity may serve as one of the predictive markers for active *H. pylori* infection.

Nodular gastritis is more frequent in children than in adults<sup>[29]</sup>. The prevalence of nodular gastritis has been reported to be 32.9%-85% in *H. pylori*-positive children<sup>[30-34]</sup>. The prevalence of nodular gastritis gradually decreased with age<sup>[13]</sup>. Our study also

showed that the patients with cardiac nodularity were significantly younger than those without cardiac nodularity. Age dependence of cardiac nodularity is in line with that of antral nodularity.

Miyamoto *et al*<sup>[13]</sup> demonstrated that atrophy scores were lower in patients with nodular gastritis than in *H. pylori*-positive controls. Nakashima *et al*<sup>[35]</sup> also reported that atrophy and intestinal metaplasia were rare in nodular gastritis. Our study also showed that compared with patients without cardiac nodularity, Intestinal metaplasia score of the patients with cardiac nodularity was significantly lower. Cardiac nodularity seemed to disappear with the progression of intestinal metaplasia.

Dwivedi *et al*<sup>[36]</sup> reported that 87.5% of nodular gastritis patients showed complete normalization of the gastric mucosa after *H. pylori* eradication therapy. Our study also showed significantly low prevalence of cardiac nodularity in *H. pylori*-eradicated patients, especially in patients who underwent eradication a long time ago. Cardiac nodularity seemed to disappear with improvement in gastric inflammation after *H. pylori* eradication.

This study had some limitations. First, this study employed only a single experienced endoscopist. Second, the study was a retrospective review at a single institution. Our results should be validated in diverse settings for generalizability.

## CONCLUSION

This report outlined the prevalence and clinical features of cardiac nodularity, and confirmed its close association with active *H. pylori* infection.

## ARTICLE HIGHLIGHTS

### Research background

*Helicobacter pylori* (*H. pylori*)-associated nodular gastritis could occur in both the antrum and the cardia. Cardiac nodularity-like appearance is found more frequently than antral nodularity.

### Research motivation

Previous study included only the patients who were evaluated for *H. pylori* infection for the first time. There still remains a lack of the prevalence and clinical features of cardiac nodularity-like appearance.

### Research objectives

We aimed to evaluate the characteristics of cardiac nodularity-like appearance.

### Research methods

We enrolled consecutive patients who underwent esophagogastroduodenoscopy between May, 2017 and August, 2019 in the Toyoshima Endoscopy Clinic. We included *H. pylori*-negative, *H. pylori*-positive, and *H. pylori*-eradicated patients, and excluded patients with unclear *H. pylori* status and eradication failure. Cardiac nodularity was defined as a miliary nodular appearance or the presence of scattered whitish circular small colorations within 2 cm of the esophagogastric junction.

### Research results

A total of 1078 patients were finally included. The prevalence of cardiac and antral nodularity in *H. pylori*-negative, -positive, and -eradicated patients were 0.14% and 0.14%, 54.5% and 29.5%, and 4.5% and 0.6%, respectively. Cardiac nodularity-like appearance was more frequent than antral nodularity in *H. pylori*-positive and -eradicated patients. Cardiac nodularity-like appearance was often found in younger patients and patients with less intestinal metaplasia. Cardiac nodularity-like appearance decreased after eradication, especially in patients who underwent eradication a long time ago.

### Research conclusions

This report outlines the prevalence and clinical features of cardiac nodularity-like appearance, and confirm its close association with active *H. pylori* infection.

**Research perspectives**

Our results should be validated in diverse settings for generalizability.

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