Nodular gastritis in association with gastric cancer development before and after Helicobacter pylori eradication

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Abstract

Background and Aim: Nodular gastritis is caused by Helicobacter pylori infection and is associated with the development of diffuse-type gastric cancer. This study examined the clinical characteristics of patients with nodular gastritis, including cancer incidence before and after H. pylori eradication.

Methods: This was a retrospective study of patients who underwent upper endoscopy and were positive for H. pylori infection. We examined the clinical findings and follow-up data after H. pylori eradication in patients with and without nodular gastritis.

Results: Of the 674 patients with H. pylori infections, nodular gastritis was observed in 114 (17%). It was more prevalent in women (69%) and young adults. Among patients with nodular gastritis, six (5%) had gastric cancer, all of which were of the diffuse type. Among the 19 (4%) patients with gastric cancer and no nodular gastritis, 16 had intestinal-type cancer. White spot aggregates in the corpus, a specific finding in patients with nodular gastritis, were more frequently observed in patients with gastric cancer than in those without (83% vs 26%, P = 0.0025). Of 82 patients with nodular gastritis who had H. pylori eradicated successfully, none developed gastric cancer over a 3-year follow-up period, while 7 (3%) of 220 patients without nodular gastritis developed gastric cancer after H. pylori eradication.

Conclusions: In patients with nodular gastritis, white spot aggregates in the corpus may indicate a higher risk of developing diffuse-type gastric cancer. Nodular gastritis may be an indication for eradication therapy to reduce the risk of cancer development after H. pylori eradication.

Introduction

Eastham et al. initially reported nodular gastritis (NG) in 1988. Endoscopic features of NG, highlighted by indigo-carmine dye spraying, show antral nodularity. Histological examination of antral nodularity showed infiltration of inflammatory cells, with large and superficially located lymphoid follicles.1–8

NG is considered a specific, but insensitive, endoscopic marker for gastric Helicobacter pylori (H. pylori) infection, which mostly occurs in children.1 Recent studies have shown that NG also manifests in adults, particularly in women and young adults, and is strongly associated with H. pylori infection.2–4,9

Observational studies of Japanese adults with NG have suggested an association with gastric cancer, particularly diffuse-type gastric cancer.3,5,10,11 However, the biological and epidemiological associations between NG and cancer development are largely unknown. Few reports exist on the differences in clinical course and cancer development between patients with H. pylori infections with and without NG.

In this study, we examined the clinical characteristics of patients with H. pylori infections, including endoscopic findings, cancer development, and follow-up data after H. pylori eradication, particularly focusing on the presence or absence of NG.

Methods

Patients. We completed a retrospective chart review of patients who underwent esophagogastroduodenoscopy (EGD) at Hidaka General Hospital between January 2006 and December 2014, focusing on differences between patients with and without NG. All patients lived in the Wakayama prefecture, in the southwestern part of Japan, where gastric cancer is prevalent. Eligible criteria were age 20 years or older and suffering from a H. pylori infection at the time of EGD. H. pylori status was not uniformly
examine patients with EGD. However, patients suspected of 
H. pylori infection due to specific EGD findings, including peptic ulcer, atrophic gastritis, intestinal metaplasia, gastric cancer, and NG, were examined. Patients who requested H. pylori examinations were examined regardless of EGD findings.

Exclusion criteria were history of stomach surgery; history of H. pylori eradication therapy; and medications with potential gastrointestinal effects, including proton pump inhibitors, H2 receptor antagonists, corticosteroids, and nonsteroidal anti-inflammatory drugs. The study design was approved by the ethics committee of Hidaka General Hospital and was reviewed annually.

**Evaluation of EGD.** EGD was performed by endoscopists with at least 7 years’ experience of upper endoscopy, using a videoscope (GIF-H260, Q260, XQ260, or XP260N; Olympus, Tokyo, Japan). Both transnasal and transoral approaches were allowed. Chromoendoscopy with 0.2% indigo carmine was applied if needed. The endoscopic definition of NG is a form of antral gastritis characterized by an unusual miliary pattern resembling “gooseflesh” (Fig. 1a,b). If NG was not definite on endoscopic appearance alone, we obtained biopsy specimens to confirm the presence of superficially located and prominent lymphoid follicles (Fig. 1c). As some patients with NG show white spot aggregates in the corpus (corpus white spots: CWS) (Fig. 1d,e), the presence or absence of this was also noted.

In addition to the diagnosis of the presence or absence of NG, we noted clinically relevant findings, including gastric cancer, peptic ulcers, gastric erosions, hyperplastic polyps, gastric submucosal tumors, gastroesophageal reflux disease, and atrophic gastritis. The severity of atrophy was classified as closed or open type according to the Kimura–Takemoto endoscopic classification system for chronic gastritis.12,13 Closed-type atrophy indicates that the leading edge of the atrophic border, starting from the greater curvature of the antrum, lies in the lesser curvature. Open-type atrophy indicates that the leading edge of the atrophic border is invisible on the lesser curvature, and the atrophic area is widespread on endoscopy, with the border extended toward the greater curvature. Gastric cancer was histopathologically assessed based on biopsy or resected specimens and classified as intestinal or diffuse type, according to the classification described by Laurén.14 Furthermore, gastric cancer was morphologically categorized as either superficial or advanced type based on the Japanese classification of gastric carcinoma: third English edition.15

All endoscopic reports and digitally stored images were reevaluated by two endoscopy specialists to confirm the presence or absence of NG and CWS.

**Evaluation and eradication of H. pylori.** We examined H. pylori infection status using serum-specific IgG H. pylori antibodies with an enzyme immunoassay kit (SRL, Tokyo, Japan), the $^{13}$C-urea breath test, and/or a rapid urease test (CLO test; Serim Research Corp., Elkhart, Indiana, USA). When one or more tests were positive, the patient was determined to be positive for H. pylori infection.

We recommended eradication therapy for patients with H. pylori infection, including NG, but the decision to receive treatment was up to each patient. Those who opted for treatment received one week of triple therapy with clarithromycin 200 mg, amoxicillin 750 mg, and a proton pump inhibitor (lansoprazole 30 mg, omeprazole 20 mg, or rabeprazole 10 mg) twice daily as the first-line regimen. We confirmed the results of the eradication therapy through the $^{13}$C-urea breath test 6–8 weeks after the regimen was completed. If the first eradication was unsuccessful, the patient underwent second-line eradication. This consisted of

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**Figure 1** Endoscopic appearance and pathological features of nodular gastritis. (a) and (b) are typical endoscopic images of nodular gastritis (NG). (a) An unusual miliary pattern resembling “gooseflesh” in the antrum. (b) Antral nodularity is highlighted with chromoendoscopy using indigo-carmine dye spraying. (c) A pathological finding of biopsy specimens from NG. Pathological findings from biopsy specimens are characterized by superficially located prominent lymphoid follicles with a germinal center (hematoxylin and eosin staining). (d) and (e) White spot aggregates in gastric corpus (corpus white spots: CWS) in a patient with NG.
Patients with *H. pylori*-positive (n = 674)

- NG group (n = 114)
  - Gastric cancer detected at first EGD (n = 6)
  - *H. pylori* not eradicated (n = 8)

- Non-NG group (n = 560)
  - Gastric cancer detected at first EGD (n = 19)
  - *H. pylori* not eradicated (n = 217)

Succeeded in eradication (n = 100)

- Loss of follow-up (n = 18)
  - Gastric cancer not developed (n = 82)
  - Gastric cancer developed (n = 0)

Succeeded in eradication (n = 324)

- Loss of follow-up (n = 104)
  - Gastric cancer not developed (n = 213)
  - Gastric cancer developed (n = 7)

**Figure 2** A schematic follow of study subjects. EGD, esophagogastroduodenoscopy; *H. pylori*, *Helicobacter pylori*; NG, nodular gastritis.

Follow-up of patients. Patients who had successful eradication therapy were followed up with EGD every 12 months. We calculated the observation period for each patient from the time of successful eradication to the time of diagnosis of gastric cancer or to the time of last surveillance.

Statistical analysis. Continuous variables were expressed as median (range), while categorical variables were presented as absolute values and percentages. We analyzed differences between continuous variables using the Mann–Whitney *U*-test, and the differences between categorical variables were analyzed using the chi-square test or Fisher’s exact test. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed with JMP 13 software (SAS Institute, Cary, NC, USA).

**Results**

Clinical characteristics of patients. Between January 2006 and December 2014, 674 patients underwent EGD with positive results for *H. pylori* infection. Of these, 114 exhibited NG, while the remaining 560 did not. Study flow is depicted in Figure 2, and clinical profiles of subjects within the two groups are shown in Table 1. Patients with NG were significantly younger than those without (48.5 [23–78] years vs 63.0 [23–94] years, *P* < 0.0001). In addition, more female patients had NG (69% vs 41%, *P* < 0.0001) than male patients. Age distributions of patients with and without NG, according to gender, are shown in Figure 3. Few patients with NG were male and older than 40 years. We did not observe this tendency with female patients. The majority of patients with *H. pylori* infections, with and without NG, showed atrophic gastritis. The degree of atrophic grade in NG subjects was significantly milder than those subjects without NG (*P* < 0.0001).

Gastric cancer in patients with NG. Of those with NG, six patients (5%) had gastric cancer (Table 2). Of these, five were females, and all cancers were diffuse-type adenocarcinoma.
localized to the corpus. A total of 19 (4%) patients without NG had gastric cancer; 12 were male, 10 had the cancer located in the antrum, and 16 had intestinal gastric cancer. Cancer involving NG developed more frequently in females and was more likely to be diffuse-type gastric cancer ($P = 0.0002$).

In patients with NG, we compared those who had gastric cancer with those who did not (Table 3). CWS was more frequently observed in patients with gastric cancer than in those without (83% vs 26%, $P = 0.0025$), suggesting that this finding is associated with cancer development from NG. No significant differences were observed in other endoscopic findings, including atrophic grade, peptic ulcer, and hyperplastic polyp, between patients with NG who had and did not have gastric cancer.

**Treatment of *H. pylori* infection and follow-up.**

Patients with and without NG post-*H. pylori* eradication were followed up after initial EGD (Fig. 2). Of 108 patients with NG who did not have gastric cancer, 100 underwent successful eradication of *H. pylori*. However, of the 541 patients without NG who did not have gastric cancer, 324 underwent successful eradication of *H. pylori*. Analysis of demographic factors, including age, gender, comorbidities, and atrophic grade, in patients receiving the follow-up (82 with NG and 220 without NG) was performed, and the results were not so different from those for the whole cohort (Table S1, Supporting information).

Of the 82 subjects with NG who were seen for follow-up, none developed gastric cancer (mean observation period, 42.6 ± 28.3 months). In contrast, of 220 subjects without NG who were seen during follow-up (mean observation period, 35.1 ± 28.5 months), 7 (3%) developed gastric cancer (male = 5, female = 2; five subjects had intestinal-type cancers, and two had diffuse-type cancer). Among the 32 patients with gastric cancer at initial EGD or throughout the follow-up, 6 developed from NG and 26 from non-NG. Cancer from NG was more likely to be observed in younger subjects ($P = 0.0037$), in females ($P = 0.030$), and in patients with a lower atrophic grade ($P = 0.0089$), dominantly presenting diffuse-type pathology ($P = 0.0002$). Meanwhile, in comparing 7 patients who developed gastric cancer during the follow-up period with 295 patients who did not, the former was significantly older than the latter ($P = 0.003$) (Table S2). These results suggest that patients with NG have a lower risk of developing gastric cancer after *H. pylori* eradication.

**Discussion**

This study confirmed the results of previous reports regarding NG, including prevalence in females and young adults and susceptibility to diffuse-type gastric cancer. In addition, we report

| Table 1 Characteristics of study subjects and endoscopic findings | Helicobacter pylori-positive |
|----------------------|-----------------------------|
|                      | Non-NG subjects | NG subjects | $P$-value |
| Subjects             |                 |             |           |
| Cases (n)            | 560            | 114     | —         |
| Median age (range) (year) | 63 (23–94) | 48.5 (23–78) | <0.0001 |
| Gender (%)           |                 |             |           |
| Male                 | 329 (59)       | 35 (31)   | —         |
| Female               | 231 (41)       | 79 (69)   | <0.0001 |
| Purpose of EGD (%)   |                 |             |           |
| Epigastric pain      | 171 (31)       | 57 (50)   | 0.0001   |
| Cancer screening     | 241 (43)       | 31 (27)   | 0.0017   |
| Nausea               | 54 (10)        | 14 (12)   | 0.39     |
| Anemia               | 46 (8)         | 1 (1)     | 0.0051   |
| Others               | 48 (8)         | 11 (10)   | 0.71     |
| Endoscopic main findings (%) |            |             |           |
| Gastric cancer       | 19 (4)         | 6 (5)     | 0.34     |
| Intestinal-type      | 16 (3)         | 0 (0)     | —        |
| Diffuse-type         | 3 (1)          | 6 (5)     | 0.0002   |
| Peptic ulcer         | 220 (39)       | 27 (24)   | 0.0016   |
| Gastric ulcer        | 147 (26)       | 19 (17)   | 0.030    |
| Duodenal ulcer       | 73 (13)        | 8 (7)     | 0.072    |
| Gastric erosion      | 28 (5)         | 4 (3)     | 0.49     |
| Hyperplastic polyps  | 19 (3)         | 0 (0)     | 0.046    |
| Gastric submucosal tumor | 3 (1)      | 2 (2)     | 0.17     |
| Gastroesophageal reflux disease | 18 (3) | 0 (0) | 0.052   |
| Atrophic gastritis   | 253 (45)       | 75 (66)   | 0.001    |
| Atrophic grade       |                 |             |           |
| Nonatrophic          | 6 (1)          | 11 (10)   | —        |
| Closed-type          | 174 (31)       | 70 (61)   | <0.0001  |
| Open-type            | 380 (69)       | 33 (29)   | —        |

Atrophic grade: according to Kimura-Takemoto classification.

EGD, esophagogastroduodenoscopy; NG, nodular gastritis.

Figure 3 Age distribution of subjects with nodular gastritis (NG) and non-NG in men (a) and in women (b). HP, *Helicobacter pylori*. [•] HPI+NG−; [□] HPI−NG−; [■] HPI+NG+. 
that new insights regarding NG-related cancer development can be obtained with meticulous endoscopic observations and follow-up of patients after \textit{H. pylori} eradication. The presence of CWS was found to be a risk factor for cancer development, and \textit{H. pylori} eradication was highly effective for the risk reduction of cancer development. Use of \textit{H. pylori}-positive and NG-negative control subjects and collection of follow-up data after \textit{H. pylori} eradication were the strengths of this investigation.

NG was previously considered to be a specific finding in children with \textit{H. pylori} infections.\textsuperscript{6,7,16} However, recent reports indicated that NG is occasionally observed in adults with \textit{H. pylori} infections,\textsuperscript{3,4,8} particularly in women and young adults. More recently, NG was observed in elderly subjects. Niknam \textit{et al.} reported 258 adult cases of patients with NG, including 35 (14\%) who were 60 years or older.\textsuperscript{17} Nakamura \textit{et al.} reported on 58 patients with NG who were at least 20 years old and found that 17 (29\%) were 60 years or older.\textsuperscript{8} The percentage of older patients in our cohort (25\%) was consistent with previous reports. Our data indicated that a relatively high percentage of \textit{H. pylori}-infected patients exhibited NG, particularly young women. Examination for NG in older patients may alter the clinical course, in association with cancer development after \textit{H. pylori} eradication, in those patients.

NG relates to cancer susceptibility. In this study, six (5\%) cases of gastric cancers, all of which were of the diffuse type, were observed in patients with NG. Previous reports indicate that NG is a risk factor for the development of diffuse-type gastric cancer in the gastric corpus,\textsuperscript{3,9-11,18,19} and our results were in line with those of previous reports. NG appears to increase the risk of developing diffuse-type gastric cancer due to highly active gastric inflammation and lower levels of atrophy. Watanabe \textit{et al.} indicated that mucosal inflammation relates to carcinogenesis for patients with \textit{H. pylori}-infected nonatrophic stomach and that higher activity of mucosal inflammation is associated with a higher risk of cancer, particularly diffuse-type cancer with higher malignant potential.\textsuperscript{20} In this context, Yoshida \textit{et al.} reported that both a higher pepsinogen II level due to active gastric inflammation and the absence of extensive atrophy were risk factors for the development of diffuse-type gastric cancer.\textsuperscript{21} Moreover, Uemura \textit{et al.} reported that many of the patients with diffuse-type gastric cancer had moderate atrophic changes and pangastritis.\textsuperscript{22}

According to our results, the grade of atrophy in subjects with NG was likely to be lower, regardless of age. In addition, previous studies reported that active inflammation was observed in the corpus mucosa of patients with NG.\textsuperscript{3} NG appears to be a specific endoscopic finding, histologically reflective of highly active inflammation with mild atrophy, both of which are risk factors for developing diffuse-type cancer.

No cancer was observed in patients with NG who completed \textit{H. pylori} eradication, while in the seven without NG (3\%), cancer developed. The higher rate of gastric cancer development after eradication compared to those of the previous studies (1–2\%)\textsuperscript{15,24} may be due to the older age of our patients (61.4 years; more than 10 years older than those of previous reports). Although \textit{H. pylori} infection is related to both intestinal- and diffuse-type cancer,\textsuperscript{22,23} the effect of \textit{H. pylori} eradication on preventing gastric cancer remains controversial. Moreover, the difference in the cancer-preventive effects of \textit{H. pylori} eradication according to cancer histology has scarcely been reported. Takenaka \textit{et al.} reported that patients, post-\textit{H. pylori} eradication, had reduced incidence of gastric cancer, particularly intestinal type, compared to patients with persistent \textit{H. pylori}.\textsuperscript{26} Take \textit{et al.} reported that diffuse-type cancer was observed only in patients post-\textit{H. pylori} eradication but not in patients where \textit{H. pylori} persisted.\textsuperscript{27} However, these results may be biased. The cohorts of both Takenaka’s and Take’s studies consisted mostly of male subjects (two-thirds of Takenaka’s population was composed of males, and Take’s population had approximately 10 times more males than females). In contrast, two-thirds of our patients with NG (55/84) were female. Diffuse-type cancer is more prevalent in women than in men,\textsuperscript{28,29} and therefore, the gender bias is a critical consideration for outcomes analyses. Our findings clearly demonstrated that \textit{H. pylori} eradication in patients with NG was effective at preventing diffuse-type cancer; however, longer follow-up studies are warranted.

### Table 2 Gastric cancer in patients with NG

| Case | Age (year) | Gender | Location | Size (mm) | Morphological type | Histopathological type | Atrophic grade | CWS |
|------|-----------|--------|----------|----------|-------------------|----------------------|----------------|-----|
| Case 1 | 35 | Female | Corpus | >50 | Type 4 | Diffuse-type | Open | + |
| Case 2 | 50 | Female | Corpus | 4 | 0-Iic | Diffuse-type | Closed | + |
| Case 3 | 51 | Female | Corpus | 15 | 0-Iic | Diffuse-type | Closed | + |
| Case 4 | 55 | Female | Antrum | 20 | 0-Iic | Diffuse-type | Open | + |
| Case 5 | 61 | Female | Corpus | 30 | 0-Iic | Diffuse-type | Closed | + |
| Case 6 | 61 | Male | Corpus | 8 | 0-Iic | Diffuse-type | Closed | – |

Atrophic grade: according to Kimura–Takemoto classification.

CWS, corpus white spots; NG, nodular gastritis.

### Table 3 NG patients with and without gastric cancer

| Cases (n) | NG with gastric cancer | NG without gastric cancer | P-value |
|-----------|------------------------|---------------------------|---------|
| Median age (range) (year) | 53 (35–61) | 45.5 (23–78) | 0.51 |
| Gender (%) | | | 0.66 |
| Male | 1 (17) | 34 (31) | |
| Female | 5 (83) | 74 (69) | |
| Atrophic grade (%) | | | 0.075 |
| Closed-type | 4 (67) | 77 (71) | |
| Open-type | 2 (33) | 31 (29) | |
| CWS (%) | 5 (83) | 28 (26) | 0.0025 |

Atrophic grade: according to Kimura–Takemoto classification.

CWS, corpus white spots; NG, nodular gastritis.
Previous studies have shown that rugal hyperplastic gastritis (RHG) is also characterized by highly active inflammation in the corpus of the nonatrophic stomach. RHG increases the risk of diffuse-type gastric cancer, particularly of the gastric corpus. \(^{(20,30,31)}\) \(H.\) pylori eradication for the prevention of diffuse-type cancer in patients with RHG has also been suggested. NG and RHG share several features. Both are characterized by increased \(H.\) pylori-induced inflammatory cell infiltration in the gastric corpus. \(^{(2,20)}\) Second, both display less atrophic change, lower gastric acid secretion, and high concentrations of serum pepsinogen II and gastrin. \(^{(2,20)}\) Finally, eradicating \(H.\) pylori improves the nodularity and hypertrophy. \(^{(3,32,33)}\) Therefore, NG and RHG harbor common biological characteristics associated with gastric inflammation and gastric cancer development. Because RHG mostly affects men, \(^{(34,35)}\) RHG may, in effect, be a male version of NG.

A striking result of this study was the link between CWS and risk of cancer development in patients with NG. The histological findings of CWS, examined via surgical specimens, included hyperplasia of lymphoid follicles with intense mucosal infiltration, similar to NG. Patients with NG and CWS have highly active inflammation of the corpus, which is implicated in the development of diffuse-type cancer. Consequently, the presence of CWS, observed during upper endoscopy for patients with NG, should be dutifully noted. Patients who display CWS should undergo urgent \(H.\) pylori eradication therapy.

This study had several limitations. First, the study was a retrospective analysis performed at a single center; our results should be validated in diverse settings for generalizability. In particular, no development of gastric cancer in patients with NG during the follow-up may be related to younger age or female dominance. The lack of the statuses of alcohol and smoking in our patients may also be a drawback. Second, the status of \(H.\) pylori infection was not consistently examined in patients undergoing EGD at our hospital, and therefore, an inclusion bias is possible. In addition, the diagnosis of \(H.\) pylori infection might not be very accurate in our study because positivity could be determined based on one test result. Third, NG was diagnosed based on endoscopic findings, without histopathological confirmation each time. In clinical practice, however, endoscopic findings are more relevant than histological findings due to the relative ease with which they are obtained. Last, the lower rate of gastric cancer development with NG may be related to younger age or female gender.

In conclusion, NG was relatively more frequently observed in older subjects with \(H.\) pylori infection, and CWS may indicate patients at a higher risk for diffuse-type gastric cancer development. The fact that no cancers developed in patients with NG after \(H.\) pylori eradication suggests that findings of NG on endoscopy are indications for eradication therapy. Prospective studies are required to verify the findings of this study.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher’s website:

Table S1. Baseline characteristics of patients who ended the follow-up.

Table S2. Baseline characteristics of patients who developed versus did not develop gastric cancer throughout the follow-up.