Endoscopic Nodular Gastritis in Dyspeptic Adults: Prevalence and Association with *Helicobacter pylori* Infection

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Key Words

Nodular gastritis • *Helicobacter pylori* • Dyspepsia

Abstract

Objective: To determine the prevalence and histological features of endoscopic nodular gastritis (NG) in adult dyspeptic patients and its relation to *Helicobacter pylori* infection. **Subjects and Methods:** A retrospective endoscopic report review of 2,142 patients identified 67 patients with NG during the period from 1 September 2006 to 31 August 2007. A subset of 32 NG patients (group 1) who had had gastric biopsies during upper gastrointestinal endoscopy and had been evaluated for *H. pylori* infection were compared to 32 age- and gender-matched dyspeptic patients. They had undergone endoscopy during the same period, which yielded normal results, and had available biopsies that were similarly evaluated for *H. pylori* infection (controls, group 2). Pertinent clinical data were obtained from the patients' records. An experienced pathologist assessed the biopsies for the presence and grade of inflammation, activity, glandular atrophy, intestinal metaplasia, presence and density of *H. pylori* and presence of lymphoid follicles or aggregates. **Results:** NG was identified in 67 (3.1%) patients. On histological examination, group 1 had a significantly higher grade of gas-

tritis ($p < 0.001$). The presence and density of *H. pylori* infection was significantly higher in group 1 ($p < 0.001$). The *H. pylori* density correlated significantly with the severity of gastritis ($r = 0.57$, $p < 0.001$). The endoscopic performance of NG on *H. pylori* infection had high specificity (96.8%) and positive predictive value (93.3%). **Conclusion:** This study outlined the clinicopathological features of NG identified among a cohort of dyspeptic patients in Kuwait and confirmed the close association with *H. pylori* infection. However, our study has a limitation in that histopathologic assessment of all NG patients was not feasible.

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Introduction

Nodular gastritis (NG) is a form of chronic gastritis that has a unique miliary pattern on endoscopy with cobblestone appearance. It has also been called nodular antiritis or gastric lymphonodular hyperplasia, based on the endoscopic features that are more common in the gastric antrum [1, 2]. It is characterized by moderate inflammation, eosinophilic infiltration into the superficial lamina propria, and lymphoid hyperplasia in the gastric mucosa [3]. Lymphoid hyperplasia and NG appear to be more fre-

quent in children than in adults. The data about the prevalence, clinical symptoms and response to therapy of NG in adults are limited [3–5]. While some investigators believe that NG may predict *H. pylori* infection and histologic gastritis [2, 6], others question its specificity [7]. We aimed to determine the prevalence and histological features of endoscopic NG in adult dyspeptic patients and its relation to *H. pylori* infection.

Subjects and Methods

This was a retrospective study. The endoscopic reports of 2,142 adult dyspeptic patients (≥ 18 years) who underwent upper gastrointestinal endoscopy at the Gastroenterology Unit of Farwaniya Hospital (a 650-bed regional hospital) from 1 September 2006 to 31 August 2007 were thoroughly reviewed by experienced staff. The unit provides inpatient and outpatient services with ~2,500 upper gastrointestinal endoscopies performed each year using a video-endoscope system (GIF-160 Diagnostic Gastro-videscopes, Olympus, Tokyo, Japan).

Of 67 patients identified with NG, 32 only (group 1) had gastric biopsies taken at the time of endoscopy and tested for *H. pylori* by rapid urease (CLO) test. The group 1 patients (13 male and 19 female) were compared to a group of 32 age- and gender-matched (13 male and 19 female) dyspeptic patients who had undergone endoscopy during the same period. Their endoscopy was normal, and they had available biopsies similarly evaluated for *H. pylori* infection. This was the control group.

The following patients were excluded: (1) those who had previously received *H. pylori* eradication therapy, individual antacids, H_2 -receptor blockers, proton pump inhibitors or antibiotics within 2 weeks prior to endoscopy; (2) those in whom the stomach could not be evaluated properly whatever the reason; (3) those who had received nonsteroidal anti-inflammatory drugs in the last 2 weeks and those who had comorbid conditions commonly causing congestive mucosal changes such as cirrhosis or uremia.

Ethical Considerations

The Standing Committee for Coordination of Health and Medical Research at the Ministry of Health, Kuwait, approved this study.

Endoscopic Diagnosis

The diagnosis of NG was made when the mucosa had an irregular cobblestone pavement. The characteristic finding was micronodules that measured 1–4 mm in diameter, had a smooth surface and the same color of the surrounding mucosa as described previously [8]. These nodules were better identified after biopsy collection because the blood from the biopsy site surrounded and highlighted them (fig. 1).

Gastric Biopsies and Histopathology

Thirty-two patients from each group in whom at least three gastric biopsies were obtained were eligible for histological analysis. All specimens were reviewed by one experienced pathologist (N.A.), who was blinded to any clinical or endoscopic information. Biopsies included one from the antrum for CLO test, one

Fig. 1. Endoscopic NG after biopsy, having the characteristic cobblestone appearance.

from the antrum within 2–3 cm of the pylorus and one from the middle portion of the greater curvature. The latter two biopsies were fixed in formalin (5–10%) and subjected to a paraffin-embedding procedure. Three to four sections, 5 μ m thick, were obtained from each paraffin block. Sections were stained with hematoxylin-eosin (HE) for histological examination and carbol-fuchsin for *H. pylori* assessment. Each tissue specimen was examined for the presence and grade of mononuclear cell infiltrate (inflammation), polymorph neutrophil infiltrates (activity), glandular atrophy, intestinal metaplasia, and *H. pylori* infection. These parameters were rated as absent = 0, mild = 1, moderate = 2, and marked = 3 according to the updated Sydney system for the classification and grading of gastritis [9] using the visual analogue scales applied to the microscopic examination. The specimen was also examined for the prevalence of lymphoid follicles or aggregates.

Diagnosis of *H. pylori* Infection

A rapid urease test (CLO test; Kimberly-Clark Ltd., Draper, Utah, USA) was performed for all patients studied. When the CLO test showed red-violet color within 24 h at room temperature, or *H. pylori* bacteria irrespective of their density were found in one or more of the biopsy specimens, the diagnosis of *H. pylori* infection was made. If both tests were negative the patient was considered *H. pylori*-negative.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Windows (version 11.0; SPSS Inc., Chicago, Ill., USA) was used for analysis of data. χ^2 or Fisher's exact test where appropriate was used for analysis of categorical variables. All tests used were two-tailed. A *p* value < 0.05 was considered as statistically significant. Spearman's correlation coefficient was used to detect any association between the severity of gastric inflammation and density of *H. pylori* infection. Diagnostic accuracy of the endoscopic findings of NG for the diagnosis of *H. pylori* infection was tested in a 2 $\times$ 2 table as described previously [10].

Results

Of the 2,142 patients (1,199 males and 943 females, ratio 14:11) who underwent upper gastrointestinal endoscopy for dyspepsia, 67 patients were diagnosed with NG at a prevalence rate of 3.1%. Of the 67 NG patients, 26 (38.8%) were males and 41 (61.2%) females. The mean age was 40 ± 12 years (range 18–66). The gender distribution of the NG cases showed a significant female preponderance in view of the gender distribution of all endoscopy patients ($p = 0.006$). The main presenting symptoms included epigastric pain: 76.1%; heartburn: 76.1%; abdominal bloating: 62.7%; nausea: 29.9% and vomiting: 22.4%. The nodular pattern was predominant in the antrum in 43 (64.2%) patients, and in both the antrum and lower body in 24 (35.8%). Associated duodenal ulcer was found in 18 (27%) patients and gastric ulcer in 3 (4%) as shown in table 1.

On histological examination, group 1 had a significantly higher grade of gastritis ($p < 0.001$) when compared with group 2 (table 2) as indicated by widespread mononuclear cell infiltration, polymorph neutrophils, and lymphoid follicles in 31 (96.9%) patients. Separate analysis showed a nonsignificant gender-associated difference in mucosal inflammation, *H. pylori* density, and lymphoid follicle numbers in GI ($p > 0.05$). A photomicrograph of NG showing marked chronic inflammation with lymphoid follicle formation is depicted in figure 2. Two patients (6.3%) in group 1 showed moderate glandular atrophy and 1 (3.1%) showed intestinal metaplasia (fig. 3).

H. pylori infection was present in 96.9% of group 1 and in 56.3% of group 2. The presence and density of *H. pylori* infection were significantly higher in group 1 than 2 ($p < 0.001$, table 2). The *H. pylori* density correlated significantly with the severity of inflammation ($r = 0.57$, $p < 0.001$). The presence of NG on endoscopy had a sensitivity of 63.3%, a specificity of 96.8%, and positive and negative predictive values of 93.3 and 43.8%, respectively, for *H. pylori* infection.

Discussion

The prevalence of NG in this study of 3.1% is similar to that of Chen et al. [11], who reported a rate of 2.9%, but is higher than the 0.05% of Chen et al. [12] and the 0.19% of Miyamoto et al. [3]. The difference could be due to the selection criteria as our sample was drawn from symptomatic patients referred for endoscopy, whereas studies

Table 1. Clinical features and endoscopic findings among 67 NG cases

Mean age $\pm$ SD, years	40.3 $\pm$ 12
Gender	
Female	41 (61.2%)
Male	26 (38.8%)
Presenting symptoms	
Epigastric pain	51 (76.1%)
Heartburn	51 (76.1%)
Bloating	42 (62.7%)
Nausea	20 (29.9%)
Vomiting	15 (22.4%)
Location	
Antral	43 (64.2%)
Antral and lower body	24 (35.8%)
Associated ulcers	
Duodenal	18 (26.9%)
Gastric	3 (4.5%)

Table 2. Histological features among NG patients and controls

Pathologic parameter	NG patients (n = 32)		Controls (n = 32)		p value
	n	%	n	%	
<i>H. pylori</i> density					
<i>H. pylori</i> -negative	1	3.1	14	43.8	<0.001
Mild	4	12.5	11	34.4	
Moderate	10	31.3	4	12.5	
Marked	17	53.1	3	9.4	
Inflammation					
Absent	1	3.1	15	46.9	<0.001
Mild	3	9.4	7	21.9	
Moderate	8	25.0	5	15.6	
Marked	20	62.5	5	15.6	
Activity					
Absent	1	3.1	14	43.8	<0.001
Mild	5	15.6	12	37.5	
Moderate	9	28.1	3	9.4	
Marked	16	50.0	3	9.4	
Glandular atrophy	2	6.3	0	0	0.492
Intestinal metaplasia	1	3.1	0	0	1
Lymphoid follicles	31	96.9	11	34.4	<0.001

that reported lower prevalence rate included symptomatic and asymptomatic individuals during screening endoscopy. Other reasons for variability in prevalence rate could be related to differences in the study design, host, bacterial or environmental factors.

Color version available online

Fig. 2. NG showing marked chronic inflammation with lymphoid follicle. HE. $\times 40$.

Color version available online

Fig. 3. Mononuclear cell infiltrate and intestinal metaplasia from a patient with NG. HE. $\times 200$.

Similar to previous studies [3, 13], we found that female patients were more commonly affected than males. This higher female proportion goes against the concept that *H. pylori* infection has no gender predilection. However, it likely supports the hypothesis that the outcome of *H. pylori* infection may relate to a host immune factor that is gender-specific. Innate and adaptive host immune responses are all important in the pathogenesis of *H. pylori* disease [14].

The histological changes in terms of the presence and grade of inflammation, activity, and lymphoid follicles were remarkable in NG patients. Earlier studies [15–18] with adult samples showed a significant correlation between the presence of lymphoid follicles in gastric mucosa and the grade and severity of gastritis.

Recent studies have shown that NG is strongly associated with *H. pylori* infection and may be associated with gastric cancer [19]. However, the pathogenesis and optimal management of NG in adults are unclear [3]. It is a common belief that the *H. pylori* CagA protein has no role in activating nuclear factor- κ B (a transcription factor that plays a crucial role in inflammation) and proinflammatory chemokines in gastric epithelial cells. The Cag pathogenicity island (Cag PAI) delivers intracellular peptidoglycan products into gastric epithelial cells, which activates the inflammatory response [20, 21]. However, Brandt et al. [22] provided evidence that the CagA protein per se is also capable of activating nuclear factor- κ B and potentiation of proinflammatory responses via the

Ras-MAP kinase pathway in a manner independent of CagA tyrosine phosphorylation. These responses in turn lead to proliferation of B cells and development of lymphoid aggregates and follicles. *H. pylori* infection also triggers interaction with a mucosal addressin cell adhesion molecule 1 (MAdCAM-1), a homing system mediating lymphocyte recruitment into mucosa-associated lymphoid tissue, also contributing to the development of NG [23].

The prevalence of *H. pylori* infection was particularly high in our NG patients as reported in previous studies [3, 11, 24]. Likewise, the specificity and positive predictive value of NG for *H. pylori* infection were high, which confirmed the findings of other investigators [6, 9, 11]. Therefore, we postulate that positive findings for endoscopic NG point to a probability of *H. pylori* infection. However, due to the low sensitivity of NG, absence of nodules does not exclude the possibility of *H. pylori* infection and histology should always be obtained for final diagnosis [7].

Rafeey et al. [25] demonstrated that the frequency of NG was related to the presence and density of *H. pylori* infection and the grade of histological gastritis. However, the reported prevalence rates of both *H. pylori* and NG vary considerably among countries and do not parallel each other [26].

The nodularity is probably related to the density of *H. pylori* at the beginning of infection so that large inoculums trigger an exaggerated immune response [16]. *H. pylori* is predominantly acquired in childhood, and NG

has frequently been found in children undergoing endoscopy [6]; however, NG is present in a minority of adult patients with *H. pylori* infection; it is unclear how and why that particular pattern develops in only a small proportion of adult patients. Variations in bacterial strains, host factors, or a complex interplay between host and bacterial factors have all been postulated as explanations [27].

H. pylori strains are genetically diverse and could be incapable of inducing constant immune response [28, 29]. Strains of *H. pylori* expressing CagA caused distinct nodularity and severe gastric inflammation in children [30]. In terms of host factors, cytokine gene polymorphisms influence mucosal cytokine expression, and an overly vigorous immune response might induce worse gastric inflammation [31]. Host polymorphism could also result in host-specific colonization or adaptation of certain bacterial strains [27].

In support of the idea that *H. pylori* infection could be the main inducer of the nodular pattern in NG, Dwivedi et al. [13] reported that 87.5% of NG patients showed complete normalization of the gastric mucosa following anti-*H. pylori* therapy. Koh et al. [32] found that the increase in gastritis score was dependent on the increase in *H. pylori* density and was significantly associated with the oc-

currence of NG. Also, Chen et al. [27] in 2008 reported that after treatment of *H. pylori*, there was a significant improvement in scores for gastritis activity, bacterial colonization and follicular gastritis.

In our study, intestinal metaplasia was found in a single patient with NG. Nevertheless, as yet, there is not enough evidence to determine whether or not NG is actually a precancerous condition. Regardless, *H. pylori* eradication is being investigated as prophylaxis against gastric malignancy, and it certainly seems reasonable to try to eradicate the organism in patients with NG [27]. Eradication has been shown to relieve symptoms of dyspepsia in NG [3], so treatment would be worthwhile for that reason alone.

Conclusion

This study outlined the clinicopathological features of NG identified among a cohort of dyspeptic patients in Kuwait and confirmed the close association with *H. pylori* infection. However, our study has limitations in that histopathologic assessment of all NG patients was not feasible.

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