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ORIGINAL ARTICLE

What Are the Clinical Implications of Nodular Gastritis? Clues from Histopathology

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Abstract There is no widely accepted histopathological definition for nodular gastritis. In this study we aim to uncover the pathologic entity responsible for the nodular appearance and to find clues about the clinical implications of nodular gastritis. Antral biopsy specimens of 160 patients with nodular gastritis and 133 patients without nodular gastritis were examined by an experienced pathologist for dysplasia, foveolar hyperplasia, inflammatory activity, intraepithelial lymphocytosis, intestinal metaplasia, and lymphoid follicle/aggregate formation, and comparative analysis was performed between the two groups of patients. The presence of intraepithelial lymphocytosis was more frequent in patients with nodular gastritis ($P < 0.05$). There was no difference between the two groups regarding the other pathological features such as presence of dysplasia, inflammatory activity, intestinal metaplasia, lymphoid hyperplasia, and *Helicobacter pylori* (*H. pylori*) infection. Increase of intraepithelial lymphocytes may contribute to formation of macroscopical nodules in this peculiar type of gastritis. Nodular gastritis would not indicate a new therapeutic approach in addition to the current measures for *Helicobacter pylori* infection.

Keywords *Helicobacter pylori* · Hypertrophic gastritis · B-lymphocytes

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Introduction

Nodularity on the gastric mucosa is a frequently encountered endoscopic finding. The term nodular gastritis (NG) is defined as antral gastritis in which endoscopic findings are characterized by miliary nodular appearance. NG is especially common in areas where prevalence of *Helicobacter pylori* infection is high [1]. On the other hand it is not known whether presence of NG poses extra risk beyond *H. pylori* infection with respect to gastric cancer and gastroduodenal disease.

There is no widely accepted histopathological definition for NG. To date the only pathological change suggested to be associated has been "lymphoid follicle formation" [2–4]. However, there are some studies revealing no relation between NG and number and presence of lymphoid follicles [5]. Additionally, in adults with *H. pylori* infection, lymphoid follicles are frequently observed in stomach without endoscopic nodularities [6]. Histopathological explanation for nodule formation might shed light on the clinical importance of this endoscopical descriptive term. It may also answer the question of whether or not these patients should be endoscopically and pathologically followed up.

In this study, we describe histopathological features of NG among patients admitted to Hacettepe University Hospital for adults in an effort to uncover the pathologic

entity responsible for the nodular appearance and to find clues about the clinical implications of NG.

Methods

One hundred sixty patients (56 men and 104 women) diagnosed as having antral NG on upper endoscopic examination at Hacettepe University Hospital between 2003 and 2006 were chosen for this study. All patients were adult (>17 years, mean age 48 years). One hundred sixty patients had antral biopsy specimens obtained.

Age- and gender-matched controls, patients without NG (133 patients; mean age 48 years, 56 men and 77 women) who had antral biopsy, were chosen at random from medical records for comparative analysis.

Each specimen, embedded in paraffin wax and cut into 4-μm-thick sections, was stained with hematoxylin and eosin (H&E) and also modified Giemsa. All sections were examined by an experienced pathologist for dysplasia, foveolar hyperplasia, inflammatory activity, intraepithelial lymphocytosis, intestinal metaplasia, and lymphoid follicle/aggregate formation. Examination of all specimens was performed by the same pathologist. Dysplasia, foveolar hyperplasia, and inflammatory activity were graded on a 0–2 scale (0: none, 1: mild, 2: severe). Intraepithelial lymphocyte density was graded on a 0–2 scale (0: none, 1: less than one lymphocyte for every five epithelial cells, 2: more than one lymphocyte for every five epithelial cells). Intestinal metaplasia was graded on a 0–2 scale (0: none, 1: focal, 2: widespread or complete). Lymphoid tissue was quantified as 0: none, 1: lymphoid aggregate, or 2: lymphoid follicle. Presence of *H. pylori* infection was determined by urea breath test (UBT), and urease test or histology.

Descriptive statistics were generated for all study variables, including mean and standard deviation (SD) for continuous variables and relative frequencies for categorical variables. Relations between subgroups were analyzed by using χ^2-test for categorical variables and by *t*-test for continuous variables. One-sided values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed with SPSS 11.0.

Results

Antral biopsy specimens showed that presence of intraepithelial lymphocytosis was more frequent in patients with NG ($P < 0.05$) while presence of foveolar hyperplasia was more frequent in patients without NG ($P < 0.05$; Table 1). There was no difference between the two groups regarding the other pathological features, such as presence of dysplasia, inflammatory activity, intestinal metaplasia, lymphoid hyperplasia, and *H. pylori* infection (Table 1). With respect to grade of intraepithelial lymphocytosis, dysplasia, inflammatory activity, and lymphoid hyperplasia there was no difference between the two groups (Table 2). Although widespread complete intestinal metaplasia was more frequent in the group with NG, the difference was not statistically significant (Table 2). Severe foveolar hyperplasia was more frequent in patients without NG. Histologically *H. pylori* was demonstrated in 57.5% of patients with NG, whereas 67.7% of patients without NG were positive for *H. pylori*. *H. pylori* was detected in 69.4% of the patients with NG and in 74.4% of the patients without NG by urea breath test, and urease test or histology. Lymphoid hyperplasia was significantly more frequent in *H. pylori* (+) patients (60.5%) than in *H. pylori* (−) patients (32.5%). Among patients with lymphoid hyperplasia (lymphoid aggregate/follicle formation) lymphoid follicle formation was significantly more frequent (36.2%) in *H. pylori* (+) patients than in *H. pylori* (−) patients (3.7%). Intraepithelial lymphocytosis was more frequent in *H. pylori* (+)

Table 1 Comparison of patients with and without nodular gastritis (NG) regarding presence of pathological features

Pathological feature	Patients with NG (%)	Patients without NG (%)	*P* value
Dysplasia	11.9	6.8	>0.05
Foveolar hyperplasia	76.3	85	<0.05
Inflammatory activity	75	83.5	>0.05
IE lymphocytosis	37.5	25.8	<0.05
Intestinal metaplasia	28.8	28.6	>0.05
Lymphoid hyperplasia[a]	53.1	51.9	>0.05
H. pylori[b]	57.5	67.7	>0.05

IE intraepithelial

[a] Lymphoid hyperplasia: lymphoid aggregate/follicle formation

[b] Only histologically detected

patients (33.3%) than in *H. pylori* (−) patients (27.7%), but the difference was not significant ($P > 0.05$). Marked lymphocytosis was more frequent in *H. pylori* (−) patients (30.4%) than in *H. pylori* (+) patients (17.1%), but the difference was not significant ($P > 0.05$). The associated histopathological features of nodular gastritis were seen at Fig. 1.

Discussion

This is one of the few reports in the literature to describe the pathological features of NG in adults. Our study is also important because of the fact that a range of pathological entities were comparatively analyzed between the two groups of patients with and without NG. Our results

Table 2 Comparison of patients with and without nodular gastritis (NG) regarding grade of pathological features

Pathological feature	Patients with NG (%)	Patients without NG (%)	*P* value
Severe dysplasia	10.5	11.1	>0.05
Severe foveolar hyperplasia	32	45.1	<0.05
Severe inflammatory activity	8.3	8.1	>0.05
Marked IE lymphocytosis[a]	18.3	24.2	>0.05
Widespread complete intestinal metaplasia	43.5	36.8	>0.05
Marked lymphoid hyperplasia[b]	28.2	33.3	>0.05

[a] Presence of more than one lymphocyte for every five epithelial cells

[b] Presence of lymphoid follicle formation

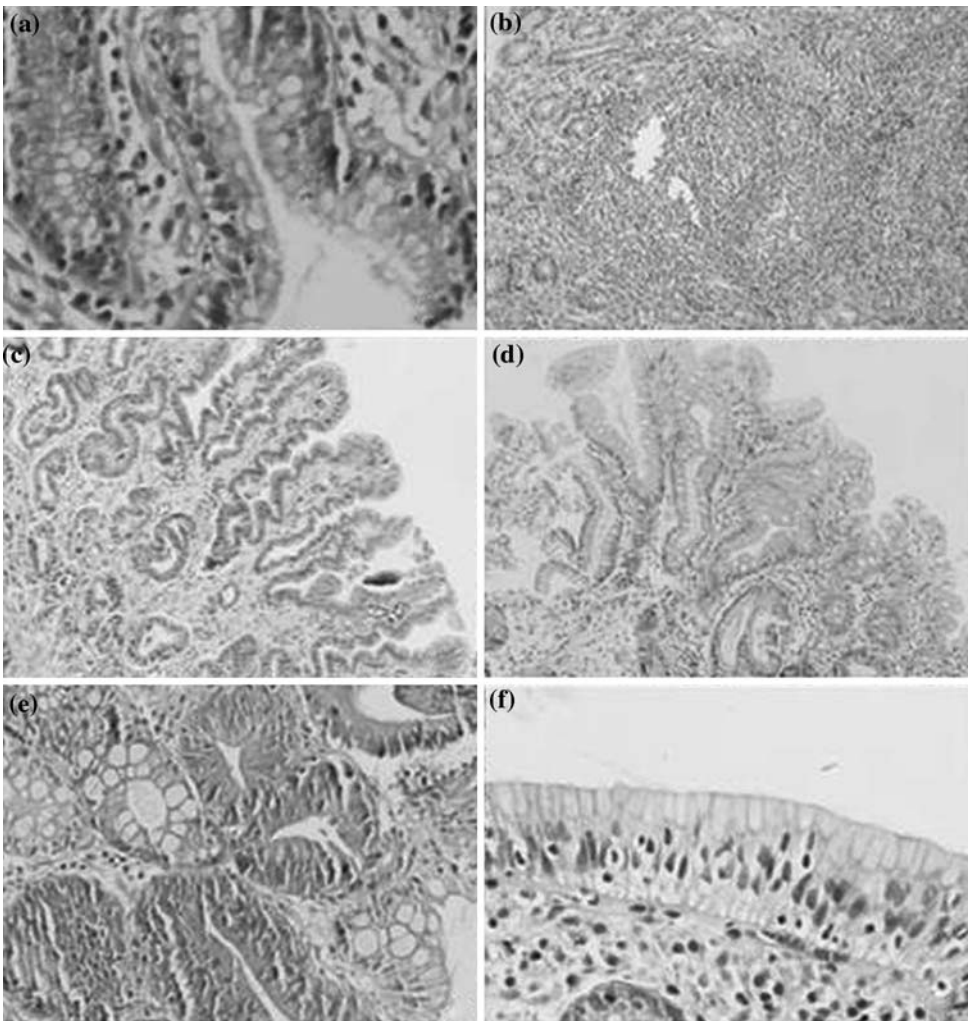

Fig. 1 Histological features of nodular gastritis: **a** *H. pylori* microorganisms seen in mucus (H&E, 400×), **b** lymphoid follicle formation (H&E, 200×), **c** foveolar hyperplasia (H&E, 200×), **d** intestinal metaplasia (H&E, 200×), **e** dysplasia (H&E, 400×), and **f** intraepithelial lymphocytosis (H&E, 400×)

showed that intraepithelial lymphocytosis might contribute to nodule formation because this pathological finding was significantly more prominent in patients with NG compared with patients without NG (Table 1).

Miyamoto et al. previously found that lymphoid follicle formation was more frequently encountered in patients with NG, and it may be the pathological finding responsible for nodule formation in these patients [2]. This hypothesis was previously supported by other authors related to NG in the pediatric age group [7]. On the other hand Maghidman et al. found in their 261-patient series that there was no relation of NG with presence and number of lymphoid follicles [5]. Our histopathological examination also revealed that lymphoid hyperplasia (lymphoid follicle/aggregate formation) was not more frequent in patients with NG. Our results are compatible with findings of a previous study which showed that, in adults with *H. pylori* infection, lymphoid follicles are frequently observed in stomachs without endoscopic nodularities [6]. We think that significant lymphoid hyperplasia may be responsible for nodule formation in some of the antral gastritis caused by *H. pylori*, but it cannot solely explain the nodules because lymphoid hyperplasia was not observed in significant number of cases (46.9%). On the other hand we found that intraepithelial lymphocytosis was not marked, although it was more frequent in patients with NG. This means that intraepithelial lymphocytosis cannot solely explain the nodules.

Presence of NG was found to show high positive predictive value for presence of *H. pylori* infection [1]. Among our patients with lymphoid hyperplasia, intraepithelial lymphocytosis, and lymphoid follicle formation (but not marked intraepithelial lymphocytosis) were more frequent in patients with *H. pylori*, indicating that intraepithelial lymphocytosis is not a precursor pathological change for the spectrum of *H. pylori*-related lymphoid proliferation, one end of which may be maltoma. And, if intraepithelial lymphocytosis is one of the factors contributing to nodule formation, patients with NG would not need follow up for the risk of maltoma.

In our series prevalence of *H. pylori* was not significantly higher in patients with NG compared with in patients without NG. On the other hand the association of NG and *H. pylori* is well known [1]. The high prevalence of *H. pylori* in our control group may have weakened the difference between the two groups regarding *H. pylori* infection.

With respect to presence and severity of inflammatory activity there was no difference between the two groups (Tables 1, 2). This indicates that inflammatory activity is not responsible for the nodular appearance, and gastroduodenal disease such as gastritis and duodenitis may not more frequently accompany this entity. The association of gastroduodenal disease and NG needs further clarification.

In our series dysplasia and widespread complete metaplasia were more frequent in patients with NG, although the difference was not significant (Tables 1,2). There are reports of gastric cancer associated with NG [7], but there were only two patients (1%) in Miyamoto's series [2] and the related reports are very rare. Although we cannot name NG as a precancerous lesion with our nonsignificant findings, we propose that nodules should be biopsied for the possibility of dysplasia and severe metaplasia to determine the type (endoscopical, pathological, both) and duration of follow-up.

Lastly, some conflicting results among studies may originate form various factors. Firstly, endoscopic identification is subjective because there is no universal consensus on the appearance of nodules. Secondly *H. pylori* is closely associated with pathological changes related to nodules, and prevalence of *H. pylori* infection varies between different parts of the world. Thirdly, all the studies in the literature have a limited number of patients and follow-up periods.

In conclusion, increase of intraepithelial lymphocytes may contribute to formation of macroscopical nodules in this peculiar type of gastritis. However, the definition and clinical importance of NG and associated histopathology could be clarified by prospective long-term follow-up studies including large number of patients. Present data give us the impression that NG would not indicate a new therapeutic approach in addition to the current measures for *H. pylori* infection [8].

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