

## Clinicopathologic Analysis of Lymphocytic Gastritis

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**Background :** Lymphocytic gastritis (LG) is defined as an infiltration of more than 25 intraepithelial lymphocytes (IELs) per 100 surface epithelial cells, and the histological differential diagnosis of LG and residual mucosa associated lymphoid tissue (MALT) lymphoma can be difficult. *Helicobacter pylori* (*H. pylori*) is regarded as one of the possible causes of LG, but its clinicopathologic features of LG have not been clarified in Korea, which has a much higher prevalence of *H. pylori* infection than Western countries. We analyzed the clinicopathologic findings of LG in Korean patients and compared the cytologic findings of IELs of LG with those of MALT lymphoma. **Methods :** Sixty six cases of LG and 59 cases of MALT lymphoma were selected and clinicopathologic features were analyzed. **Results :** Eighteen cases (27.3%) of LG were found to be associated with *H. pylori* infection. The IELs in LG were found to diffusely and regularly infiltrate in the epithelium, but MALT lymphoma showed patchy IELs. IELs in LG and MALT lymphoma were CD 8+T lymphocytes and CD20+B lymphocytes, respectively. The mean nuclear size of IELs in LG was 4.37  $\mu\text{m}$ , which was significantly smaller than those in MALT lymphoma (5.19  $\mu\text{m}$ ). **Conclusion :** LG, a rare variant of chronic gastritis is partly associated with *H. pylori* infection and more complex unknown causative factors. In addition to the immunophenotyping, the nuclear sizes of IELs can be helpful in the differential diagnosis of LG and residual MALT lymphoma.

**Key Words :** Lymphocytic; MALT lymphoma; *Helicobacter pylori*

Lymphocytic gastritis (LG) was first described in 1986 and is characterized by the infiltration of more than 25 intraepithelial lymphocytes (IELs) per 100 surface epithelial cells.<sup>1</sup> This infiltration was first considered to be associated with specific endoscopic features, such as erosions and prominent mucosal folds, and was described as so-called varioliform gastritis.<sup>2</sup> But LG has been found to have variable endoscopic findings, such as, normal mucosa, dyspeptic patients, gastric adenocarcinoma, primary gastric lymphoma, gastrointestinal protein loss, and celiac sprue.<sup>3-5</sup>

Gastric mucosa associated lymphoid tissue (MALT) lymphoma is also known to be related to *H. pylori* infection, and shows intraepithelial lymphocytic infiltration in crypt epithelium (lymphoepithelial lesion). LG may be concurrently detected with gastric MALT lymphoma and is usually identified in follow-up biopsies after MALT lymphoma after the treatment of MALT lymphoma.<sup>3</sup> Occasionally, intraepithelial lymphocytosis mimicking a lymphoepithelial lesion in MALT lymphoma is noted in an LG biopsy. The identification of residual gastric MALT lymphoma has an influence on therapeutic plans, including medication and follow up. Thus, it is necessary to discriminate between LG and residual MALT lymphoma.

In Korea, the prevalence of *H. pylori* infection and *H. pylori* associated gastritis are substantially higher than in Western countries.<sup>4</sup> A histopathologic diagnosis of chronic gastritis is mainly made using the Sydney system, in which the intensity of mononuclear cell infiltration is described, but the location of this mononuclear cell infiltration is not stated. As a result, LG has not been diagnosed actively and the clinicopathologic features of LG have not been analyzed.

Therefore, in the present study, we analyzed the clinical features, including the endoscopic findings and associations with *H. pylori* infection to determine the clinicopathological features of LG in Korea. In addition, the characteristics of IELs in LG were compared with those of MALT lymphoma to facilitate the differential diagnosis of LG and residual MALT lymphoma.

## MATERIALS AND METHODS

We collected 66 cases of LG and 59 cases of gastric MALT lymphoma, from the surgical pathology file of the Asan Medical Center from January 2001 and June 2006. All tissues were fixed in 10% buffered formalin and embedded in paraffin. Two

pathologists independently reviewed the histopathologic features of gastroscopic biopsy specimens stained with hematoxylin and eosin (H&E).

We reviewed patient medical records for; age, sex, accompanying gastrointestinal symptoms, treatment for the eradication of *H. pylori*, sites of endoscopic biopsy, and endoscopic findings. Gastroscopic biopsy specimens were examined for the presence of *H. pylori*. In most cases, endoscopic biopsies were performed randomly including abnormal mucosal areas. *H. pylori* was considered present in each cases when it was identified in H&E stained slides or positive immunostaining for *H. pylori* was noted. This principle was applied to all gastroscopic biopsies including randomly obtained gastric tissues. Serologic testing for *H. pylori* was not performed. A campylobacter like organism (CLO) gel test was carried out in seven cases, and one of these produced a positive reaction.

Immunohistochemical stainings for CD3, CD4, CD8, CD20, and CD79a were performed in 29 cases of LG and 10 cases of MALT lymphoma to determine the subtypes of lymphocytes in the epithelium. All immunostainings were performed using a Benchmark automatic immunostaining device (Ventana Medical Systems) using formalin fixed, paraffin-embedded tissue sections. Briefly, 5  $\mu$ m thick sections were obtained by microtome, transferred into adhesive slides, and dried in 62°C for 30 min. After incubation with primary antibodies against CD3 (1:500, NOVO, Newcastle, UK), CD4 (1:50, NOVO), CD8 (1:200, DAKO, Glostrup, Denmark), CD20 (1:2000, NOVO), and CD79a (1:100, DAKO), immunodetection was performed using biotinylated anti-mouse immunoglobulins, followed by peroxidase-labeled streptavidin in LSAB kit with 3,3'-diaminobenzidine chromogen as substrate. Tonsil tissue was used as positive control and was treated similarly. Primary antibodies were omitted in negative controls.

Table 1. Classification of LG in accordance with sydney system

	Absent	Mild	Moderate	Marked	Not assessed
<i>H. pylori</i>	49 (74.2%)	11 (16.6%)	3 (4.6%)	3 (4.6%)	-
Neutrophils	27 (40.9%)	18 (27.3%)	14 (21.2%)	7 (10.6%)	-
Mononuclear cells	1 (1.5%)	11 (16.6%)	47 (71.2%)	7 (10.7%)	-
Atrophy	14 (21.2%)	6 (9.1%)	6 (9.1%)	1 (1.5%)	39 (59.1%)
Intestinal metaplasia	56 (84.8%)	6 (9.1%)	1 (1.5%)	3 (4.6%)	-

LG, lymphocytic gastritis; *H. pylori*, *Helicobacter pylori*.

We measured the nuclear sizes of IELs in LG and MALT lymphoma using ImageTool version 3.00. The sizes of notch marks of hemocytometer were calibrated in high power field ( $\times 400$ ) and used as a reference size. The nuclear diameters of 10 IELs were measured in high power fields ( $\times 400$ ). To obtain more accurate measures of size, these procedures were repeated three times, and subsequently mean nuclear size was used for the statistical analysis.

Statistical analysis was performed to compare infiltrating lymphocyte nuclear sizes in LG and MALT lymphoma using the T-test in SPSS version 10.0 (SPSS, Inc., Chicago, USA). *p*-values of  $<0.05$  were considered significant.

## RESULTS

### Demographics of LG patients

The ages of LG patients ranged from 20 to 82 years (mean age: 48.8 years). The male to female ratio was 2.3:1 (46:20). Forty-four cases presented with dyspepsia and indigestion and 22 cases were discovered during a routine health examination with no specific gastrointestinal symptoms

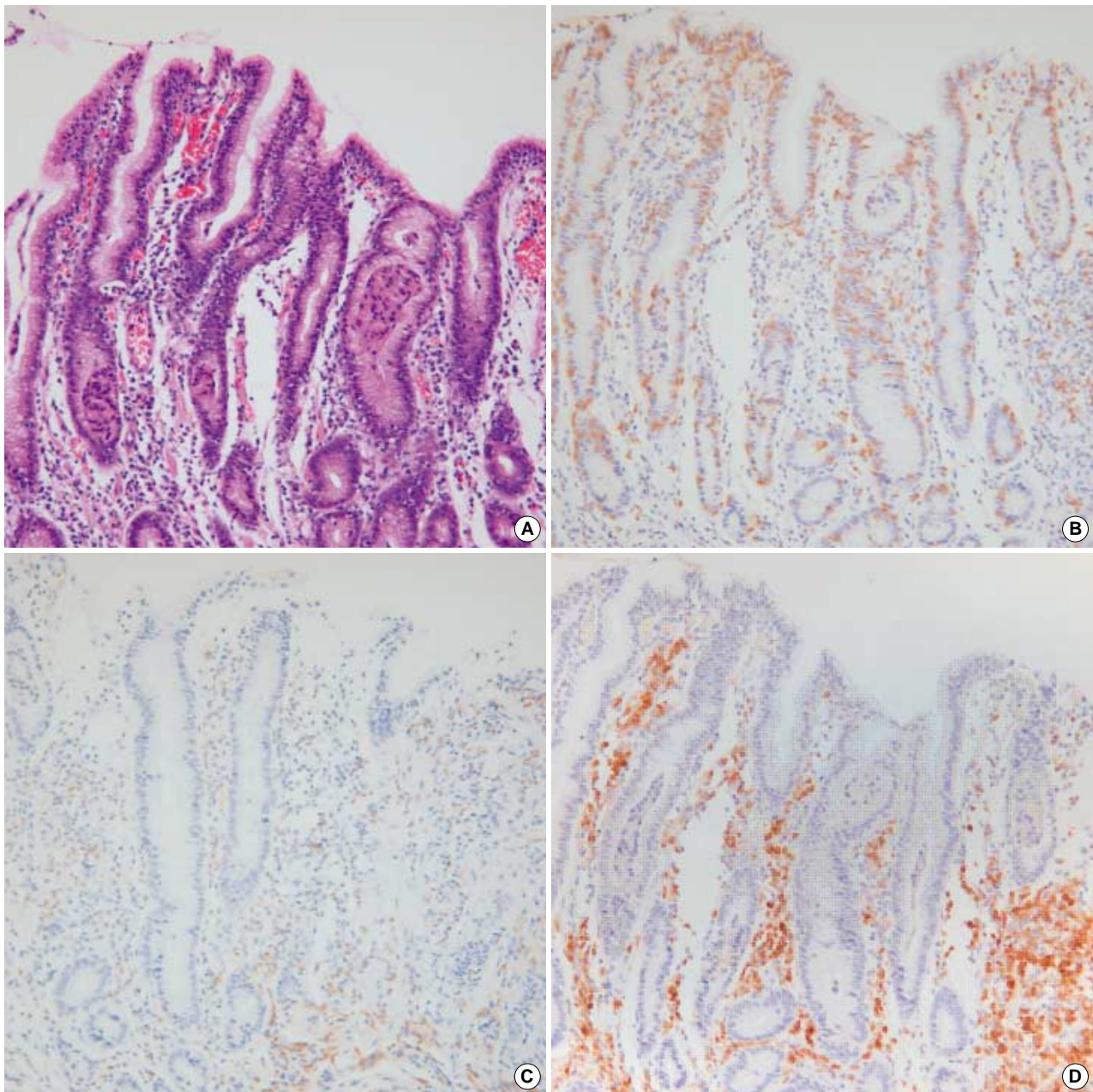
Three patients of the 66 cases with LG were associated with gastric MALT lymphoma. LG was detected in follow-up biopsies in two cases of MALT lymphoma and was concurrently observed with MALT lymphoma in one case. Two cases of gastric adenocarcinoma also occurred in association with LG at the time cancer was diagnosed.

Sixty-six cases of LG were evaluated using the Sydney system (Table 1). *H. pylori* was detected variably in 17 cases (25.8%). Neutrophils were present in 39 cases (59.1%), among which 18 cases (27.3%) were mild, 14 cases (21.2%) were moderate and 7 cases (10.6%) were severe. Mononuclear cells were observ-

Table 2. Follow-up data of patients with LG

Case number	<i>H. pylori</i>	<i>H. pylori</i> treatment	Follow-up duration (month)	Follow-up result
1	-	yes	10	Residual LG
2	-	no	2	Resolution
3	-	no	10	Resolution
4	-	no	12	Residual LG
5	-	no	34	Resolution
6	+	no	31	Resolution
7	+	no	13	Resolution
8	+	no	52	Resolution

LG, lymphocytic gastritis; *H. pylori*, *Helicobacter pylori*.



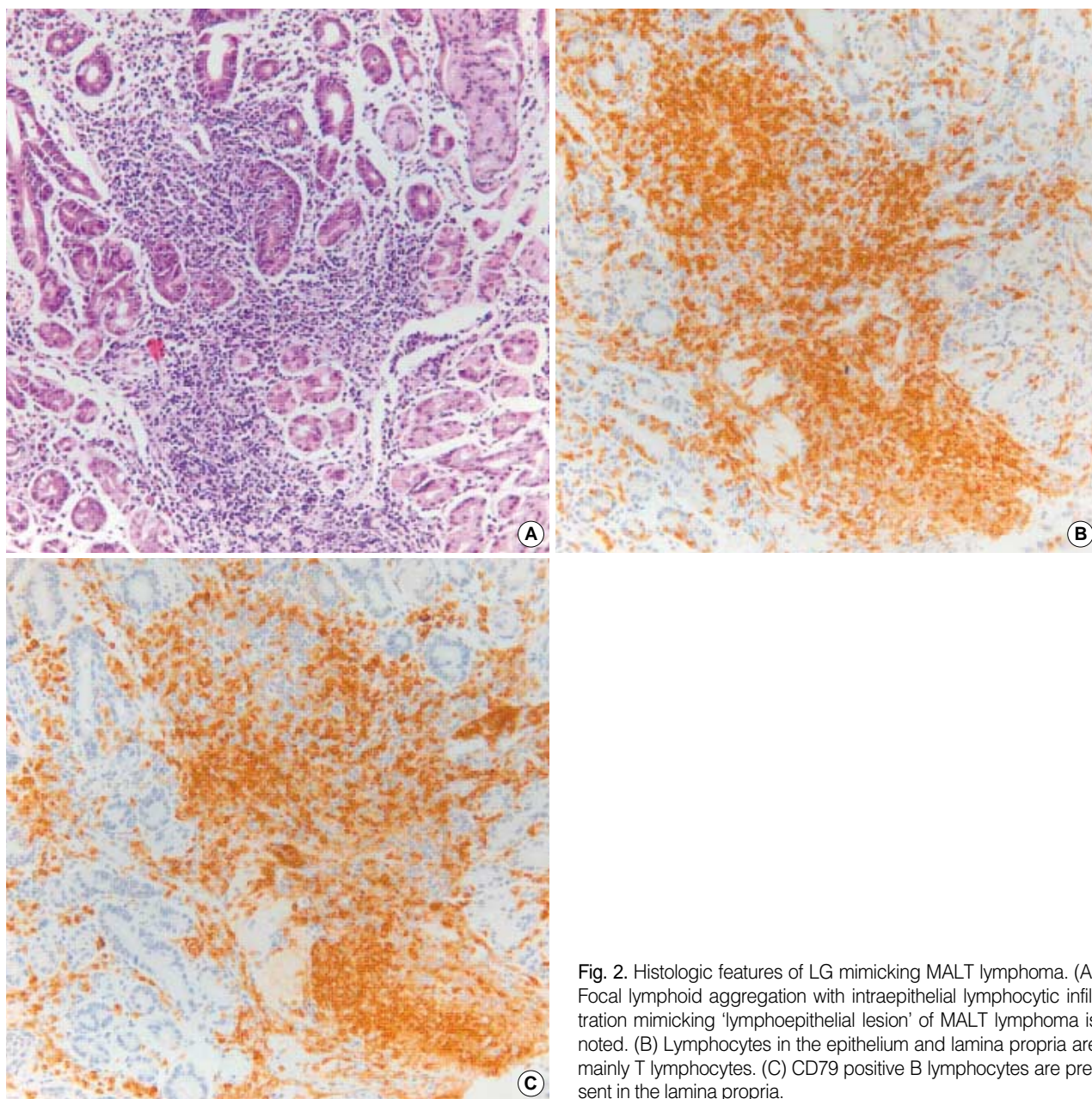
**Fig. 1.** Microscopic findings of LG. (A) Diffuse lymphocytic infiltration with peri-lymphocytic halo is identified in surface and crypt epithelium. (B) Intraepithelial lymphocytes are CD8 positive T lymphocytes. Lymphocytes in the lamina propria are CD4 positive T lymphocytes (C) and CD79 positive B lymphocytes (D).

ed in 65 cases (98.5%): 11 cases (16.6%) were mild, 47 cases (71.2%) were moderate, and 7 cases (10.7%) were severe. Atrophy was identified in 13 cases (19.7%), and intestinal metaplasia was associated with atrophy in 10 other cases (15.2%). In 39 cases (59.1%), the presence of atrophy could not be evaluated properly due to disoriented tissue embedding or a tangential section.

Fifteen cases of LG received triple therapy for *H. pylori* eradication.

Triple therapy was started empirically before LG detection in seven of these cases, and was commenced after LG diagnosis in the other eight.

A follow-up biopsy was performed in eight cases of LG (12.1%) and three of these cases were found to be associated with *H. pylori* infection. These *H. pylori* proven cases did not subsequently receive *H. pylori* eradication treatment. Six cases of LG (9.1%) resolved without any *H. pylori* treatment, one case had residual



**Fig. 2.** Histologic features of LG mimicking MALT lymphoma. (A) Focal lymphoid aggregation with intraepithelial lymphocytic infiltration mimicking 'lymphoepithelial lesion' of MALT lymphoma is noted. (B) Lymphocytes in the epithelium and lamina propria are mainly T lymphocytes. (C) CD79 positive B lymphocytes are present in the lamina propria.

LG 10 months after the treatment, and one untreated case showed persistent LG (Table 2).

#### Endoscopic findings of LG patients

The endoscopic findings of LG were variable. Erosion with or without mucosal elevation was most frequently observed in 36 (54.5%) of 66 cases, and other findings included ulcer (6 cases, 9.1%), edematous change (5 cases, 7.6%), atrophy (5 cases, 7.6%), polyp (4 cases, 6.1%), ulcer scar (3 cases, 4.5%), hyperemic lesion (3 cases, 4.5%), elevated lesion (2 cases, 3.05%).

No definite changes were observed in 2 cases (3.05%).

Lesions were detected in the body (39 cases, 59.1%), antrum (19 cases, 28.8%), angle (5 cases, 7.6%), fundus (2 cases, 3.0%), and cardia (1 case, 1.5%).

#### Relationship between LG and *H. pylori*

A total of 18 LG cases (27.3%) were associated with *H. pylori* infection. The presence of *H. pylori* was confirmed in gastroscopic biopsies in 17 cases and by CLO gel test in one case. LG was detected consecutively by follow-up biopsy after the iden-

**Table 3.** Histopathologic differences of IELs between LG and MALT lymphoma

	LG	MALT lymphoma
Location	Surface and foveolar epithelium	Mainly foveolar epithelium
Distribution	Diffuse and regular infiltration	Patchy infiltration
Perinuclear halo of IELs	+	-
Accompanied Epithelial change	-	Distortion of glandular structure Glandular epithelial degeneration
Immunophenotype of IELs	CD8 positive T lymphocytes	CD20/79 positive B lymphocytes
Nuclear size of IELs (p-value<0.001)	4.37 $\mu$ m	5.19 $\mu$ m

IELs, intraepithelial lymphocytes; LG, lymphocytic gastritis; MALT lymphoma, mucosa associated lymphoid tissue lymphoma.

tification of *H. pylori* infection in nine cases (13.6%); one of these patients showed no evidence *H. pylori* in a follow-up biopsy. In eight cases, LG and *H. pylori* co-existed.

#### Characteristics of intraepithelial lymphocytes in LG

Lymphocytic infiltration was noted in the lamina propria and in surface and foveolar epithelia. Lymphocytes in LG had diffusely and regularly infiltrated the surface and crypt epithelium and showed only a peri-lymphocytic halo without gastric epithelial changes. Lymphoid follicles were occasionally identified in the lamina propria. The mean number of intraepithelial lymphocytes per 100 epithelial cells was 47.4 (SD=14.79). Infiltrating lymphocytes in the epithelium had smaller and more hyperchromatic nuclei than gastric epithelial cells and had a peri-lymphocytic clear halo. IELs were exclusively CD8-positive T lymphocytes, while the lymphocytes in the lamina propria were CD4-positive T cells and B lymphocytes (Fig. 1). The mean nuclear size of intraepithelial lymphocytes in LG was 4.37  $\mu$ m, which was significantly smaller than that of lymphocytes in the lymphoepithelial lesions of MALT lymphoma (5.19  $\mu$ m) (p-value<0.001) (Fig. 2). These histopathologic differences between the IELs of LG and MALT lymphoma are shown in Table 3.

## DISCUSSION

In the present study, we describe for the first time the clinical and histopathologic features of LG in Koreans. Since LG

was initially described in 1986, there has been much debate as to whether it is an independent histopathologic entity.<sup>5</sup> Because a close relationship has been emphasized between LG and *H. pylori* infection in several studies and the prevalence rate of *H. pylori* infection is higher in Korea than in Western countries, LG would be expected to be more frequent. However, the prevalence rate of LG in chronic gastritis (1.02%) in the present analysis was lower than that in Western countries (4.5%).<sup>6</sup> This finding suggests that LG does not always occur as a direct result of *H. pylori* infection, but that it is associated with more complicated etiologic factors. In the present cases, the male to female ratio (2.3:1) differed from that of a previous study, which found a male to female ratio of 0.8.<sup>5</sup> The reason for this difference is not known.

LG was initially considered to be associated with the specific endoscopic finding of varioliform gastritis.<sup>7</sup> However, it is now clear that LG may be associated with various endoscopic appearances, including a normal mucosal surface.<sup>8</sup> In previous reports, erosion with or without elevation was the most frequent feature, and there was no acute accompanying inflammatory reaction. The variety of endoscopic features observed in the present study is similar to those reported in the West.

Associations between LG and hypertrophic gastropathy with protein loss and Menetrier's disease have been suggested to be important from the pathogenetic point of view.<sup>7-9</sup> Nevertheless, despite the close association between Menetrier's disease and protein-losing gastropathy and LG, histopathologic differences between these two conditions were demonstrated by Wolfsen *et al.*<sup>10</sup> Menetrier's disease is characterized by marked foveolar hyperplasia, fundic gland atrophy, mucosal edema, and minimal inflammation. In contrast, LG shows mild foveolar hyperplasia, normal fundic glands, and chronic inflammation with prominent intraepithelial lymphocytosis.<sup>10</sup> No case of Menetrier's disease was encountered in the present study according to gastroduodenoscopic biopsy findings.

The etiology of LG is not known, although *H. pylori* has been suggested to be a causative pathogen, and that LG may be a manifestation of an immunologic reaction to *H. pylori* infection.<sup>6</sup> Once gastric mucosa has been infected with *H. pylori*, the immunologic repertoire of gastric T cells is variable as it depends on environmental and/or host genetic factors. Moreover, *H. pylori* infection may cause a long-lasting T cell response. In some patients, immunologic response to *H. pylori* induces the growth of specific T cells that facilitate B cell proliferation, and increase the likelihood of MALT lymphoma.<sup>11</sup> In the present study, 9 cases (13.6%) were diagnosed after *H. pylori* infection had been

identified. The interval between the detection of LG and *H. pylori* infection ranged from 1 month to 96 months (mean: 27 months). These results support the notion that LG is a microscopic manifestation of a delayed immunologic reaction to *H. pylori* infection.

In the present study, a relatively low prevalence rate for *H. pylori* infection (27.3%) was observed in Korean LG patients. Several studies in Western countries have found similar rates (28–41%), although the prevalence of *H. pylori* infection in the West is substantially lower (<20%) than in Korea.<sup>6,10,12,13</sup> Regarding the high morbidity of *H. pylori* infection in Korea, factors other than *H. pylori* infection should be considered as etiologic factors of LG.

Long-term follow up data on LG is rare. Niemela *et al.*<sup>14</sup> reported that spontaneous healing developed in 22% of patients with LG during a 10 year of follow-up. In our study, six (85.7%) of seven cases that were untreated after LG had been diagnosed, experienced spontaneous resolution according to follow-up biopsy results (2–52 months, mean duration: 23.6 months). These findings suggest that treatment of *H. pylori* does not affect the course of LG. The spontaneous healing rate in the present study was much higher than those previously reported, but the number of cases included in the follow-up was inadequate, and further study on spontaneous healing of LG is necessary. Some studies have addressed the effect of eradication *H. pylori* therapy in LG patients. Mueller *et al.*<sup>15</sup> reported the healing of LG after *H. pylori* therapy in 93% of histologically *H. pylori*-proven patients and in 84% of histologically *H. pylori*-undetected patients. A randomized, double-blind, placebo-controlled study showed long-lasting healing of LG following *H. pylori* eradication therapy, and the healing rate of LG 12 months after triple therapy (omeprazole 20 mg b.i.d, clarithromycin 500 mg b.i.d, amoxicillin 1,000 mg b.i.d) was significantly higher (95.8% vs 53.8%,  $p$ -value=0.01) compared with omeprazole/placebo.<sup>16</sup> These findings provide evidence that emphasizes the etiological role of *H. pylori* in LG. In the present study, one case treated after a diagnosis of LG demonstrated residual LG in a follow-up biopsy, whereas six cases that were untreated were free of LG according to follow-up histological examinations. Although the number of LG cases that underwent follow-up biopsy was small, it is difficult based on our data to recommend *H. pylori* eradication therapy in LG.

Griffiths AP *et al.*<sup>3</sup> observed that LG was more prevalent in patients with gastric adenocarcinoma (12.3%) or primary gastric lymphoma (13.7%) than in the general population, which suggests that LG may be associated with an increased risk of

developing gastric lymphoma or adenocarcinoma. However, in the present study the morbidity rate of LG in cases of gastric adenocarcinoma was much lower, while that of MALT lymphoma was similar to rates reported in the West. The finding that LG was more prevalent in patients with gastric MALT lymphoma suggests that LG and gastric MALT lymphoma have a common pathogenesis. Prolonged exposure to *H. pylori* might induce an overgrowth of B cells due to T cell stimulation, and thus, facilitate the neoplastic transformation of B cells and the development of gastric MALT lymphoma.<sup>11</sup> With respect to these features, it appears that LG should naturally be accompanied by MALT lymphoma.

Two cases of LG that occurred during or after MALT lymphoma treatment led us to compare the characteristics of IELs under these two circumstances, to identify objective differences between the two that might be used for the diagnosis of residual MALT lymphoma. Although intraepithelial infiltration of lymphocytes is a common feature in both LG and MALT lymphoma, there are obvious differences between the IELs associated with the two conditions. First, the lymphocytes of LG infiltrate diffusely and regularly in the surface epithelium, while those of MALT lymphoma are scattered, usually in crypt epithelial cells. Moreover, in LG, IELs are associated with an occasional perinuclear halo without gastric epithelial changes, whereas in MALT lymphoma, IELs are always accompanied by architectural destruction of glands and degenerative changes in epithelial cells. In terms of the cytological characteristics of IELs, nuclear size was found to be objectively different in LG and MALT lymphoma, to the extent that it could be used as an adjunctive diagnostic criterion for the diagnosis of residual MALT lymphoma.

In conclusion, LG is a rare, but distinct pathologic entity of chronic gastritis. Moreover, its pathogenetic mechanism appears to be associated with a combination of *H. pylori* infection and other more complex causative factors. Cytological evaluations of intraepithelial lymphocytes, with respect to nuclear size and immunophenotyping, are necessary during evaluations of follow-up gastroscopic biopsy specimens, to differentiate LG from residual MALT lymphoma.

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