Ten year follow up study of lymphocytic gastritis: further evidence on *Helicobacter pylori* as a cause of lymphocytic gastritis and corpus gastritis

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**Abstract**

**Aims**—To examine the course of lymphocytic gastritis and its relation to *Helicobacter pylori* (*H. pylori*) infection in a 10 year follow up.

**Methods**—Ninety six patients were originally examined for dyspepsia in 1981. Gastroscopies with stepwise biopsies were performed on all the patients initially and after an interval of 10 years.

**Results**—Nine per cent of the patients (9/96) had features of lymphocytic gastritis in gastric biopsy at the first examination, and 12·5% (12/96) at the second examination; 7/9 patients (78%) had persistent lymphocytic gastritis during the follow up; in two the diagnostic features of lymphocytic gastritis had disappeared, and five had a new diagnosis of lymphocytic gastritis at the second examination. At the second examination 9/12 lymphocytic gastritis patients (75%) were *H pylori* positive histologically, while all had specific antibodies to *H pylori*. The lymphocytic gastritis patients had higher grades of gastritis (*p* = 0·009), neutrophilic and eosinophilic granulocytes, mononuclear inflammatory cells, and foveolar hyperplasia in the corpus mucosa, but smaller numbers of *H pylori* than the *H pylori* positive patients without lymphocytic gastritis. The appearance of lymphocytic gastritis during the 10 year interval was associated with increases in the grades of corpus gastritis and neutrophilic granulocytes (*p* = 0·043 for both). During the follow up, the patients with lymphocytic gastritis, but not the *H pylori* positive patients without lymphocytic gastritis, appeared to have a significant increase in the grade of intestinal metaplasia in the corpus mucosa (*p* = 0·043).

**Conclusions**—In some patients *H pylori* may cause a gastritis that predominates in the corpus and is associated with an increase in the intraepithelial lymphocyte count. This form of gastritis may cause progression of intestinal metaplasia.

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Keywords: Follow up, *Helicobacter pylori*, lymphocytic gastritis.

Lymphocytic gastritis is a histological entity characterised by a marked increase in the number of intraepithelial lymphocytes (IEL) in the gastric mucosa. The histopathological diagnosis has been shown to be associated with endoscopic findings of gastric erosions and hypertrophic gastropathy and diagnoses of protein losing gastropathy, coeliac disease, gastric adenocarcinoma, and primary lymphoma. The cause of lymphocytic gastritis is not known, but *Helicobacter pylori* (*H pylori*) has been detected histologically or serologically in 40–80% of the cases. The increase of IEL in lymphocytic gastritis is associated with an inflammatory cell infiltrate in lamina propria, but information on other histological features, such as glandular changes or intestinal metaplasia, is lacking. Furthermore, most of the data available come from cross sectional studies, and the long term course of lymphocytic gastritis is still largely obscure. In this study, we examined the course of lymphocytic gastritis, the histological features associated with it, and their relations to *H pylori* infection in a 10 year follow up.

**Methods**

**Patients**

The original series consisted of 140 unselected patients with dyspepsia aged 40–71 years referred to the gastroenterological unit of the department of internal medicine, Oulu University Hospital, for elective gastroscopy in 1981–1982. The results of the primary examinations have been published previously. The patients were invited for re-examination in 1991. Ninety six patients (40 men and 56 women, aged 49–80 years, mean age 63 (SD 8) years, 69% of the original series and 79% of those still alive) complied with the invitation and were re-examined.

Gastroscopy was performed on all the patients. Four biopsies were taken systematically from specified locations in the antrum and four in the corpus during the primary and follow up endoscopies. A questionnaire was used to record the endoscopic diagnoses, the history of abdominal and other diseases, and the use of drugs for gastric and other diseases, particularly the use of antimicrobial drugs.

The research design was approved by the ethics committee of the Faculty of Medicine, University of Oulu, Finland.

**Histopathological Methods**

The biopsies were fixed in formalin and stained with haematoxylin and eosin (H and E). The...
sections were interpreted by one pathologist (TKa), who was unaware of the clinical or endoscopic findings. The primary and follow up specimens were studied separately. The diagnosis of lymphocytic gastritis was based on the presence of IEL in a ratio of 30/100 epithelial cells or more. The number of IEL was graded as follows: grade 0 (a ratio ≤5/100), grade 1 (6–15/100), grade 2 (16–29/100), and grade 3 (≥30/100 = lymphocytic gastritis). The areas of maximum concentration of IEL in surface and foveolar epithelium were used for grading. In most cases grades were assigned subjectively, without counting the exact numbers of IEL. However, in cases which, according to subjective estimation, fell in the border zone between two grades, 100–200 cells in continuous areas were counted, and grade was assigned according to mean intraepithelial lymphocyte count per 100 epithelial cells. In addition, similar counts were made in all cases assigned to grade 3 to confirm the diagnosis of lymphocytic gastritis. The grades of gastritis, the contents (described as grades) of the different types of inflammatory cells, and the grades of foveolar hyperplasia and intestinal metaplasia were analysed separately from four stepwise biopsies from both the antrum and the corpus for each subject, and the four grades were taken as the respective grades to represent the antrum and the corpus, as described elsewhere.10–12 Gastritis grade 0 was normal, grade 1 indicated superficial gastritis, and grades 2, 3, and 4, slight, moderate, and severe atrophy.10–12

The number of lymphoid follicles in each specimen was counted and the mean number per specimen was calculated for the antral and corpus mucosa. A lymphoid follicle was defined as an aggregate of lymphocytes with a germinal centre.

The presence and quantity of H pylori were assessed by another pathologist (TKe), mostly from sections stained with Warthin-Starry (WS) (except for the 12 clearly H pylori positive cases, where representative H and E stained sections were used). This pathologist was blinded to all other information. The quantity of H pylori in each biopsy specimen was scored according to Marshall et al.13 on a four point scale from 0 (no bacteria) to 3 (numerous bacteria). The mean score for H pylori in the four antral or four corpus biopsies was taken respectively.

### SEROLOGICAL METHODS

The serological diagnosis of H pylori was made on the basis of the samples collected in 1991 by testing the specific IgG antibodies with an enzyme linked immunosorbent assay (ELISA, Pyloriset®, Orion Diagnostica, Finland).

### STATISTICS

The results were evaluated statistically using the Wilcoxon matched pairs signed ranks test and the Mann-Whitney U test. A probability of p<0.05 in two tailed tests was considered statistically significant. The analyses were made with the Statistical Package for Social Sciences (SPSS).

### Results

Nine of the 96 patients (9%) had lymphocytic gastritis at the first examination in 1981 (group LG1, three men and six women aged 42–61 years, mean 52 (7) years). Seven of them (78%) had persistent lymphocytic gastritis at the time of the follow up examination, most commonly in the corpus mucosa (figs 1 and 2). In addition, five patients had an increase in the numbers of IEL, compatible with the criterion for lymphocytic gastritis at the follow up. Thus 12 patients (12.5%) had lymphocytic gastritis at the second examination in 1991 (group LG2, three men...
and nine women aged 51–71 years, mean 61 (7) years.

During the 10 year follow up, the LG1 patients were found to have decreases in the grades of antral neutrophilic granulocytes (p=0.042) and antral and corpus foveolar hyperplasia (p=0.028 and p=0.035, respectively) (table 1). The grade of intestinal metaplasia increased (p=0.043) in the corpus mucosa. In addition, the numbers of H pylori in the corpus mucosa decreased significantly (p=0.028).

The changes in the gastric mucosa of randomly taken age and sex matched controls with H pylori positive gastritis (group non-LG1, three men and six women aged 42–62 years, mean 53 (6) years) were partly comparable to those seen in the patients with lymphocytic gastritis (table 1). In contrast to the changes seen in the patients with lymphocytic gastritis, however, the antral neutrophilic granulocyte grade slightly increased, while the intestinal metaplasia grade in the corpus mucosa did not change significantly. In addition, no significant changes in the numbers of H pylori in either the antral or the corpus mucosa were noticed. The number of lymphoid follicles in the gastric mucosa did not change significantly in either lymphocytic gastritis or non-lymphocytic gastritis patients (data not given here).

Two patients had healed lymphocytic gastritis (a decrease in the grade of intraepithelial lymphocytes below grade 3 at the second examination). A 61 year old male had had a mild H pylori negative gastritis at the first examination. This patient’s grade of antral gastritis had decreased from 0.75 to 0.25 and grade of corpus gastritis from 1.33 to 0, while the patient remained H pylori negative. A 65 year old male had had histologically positive H pylori gastritis at the first examination and his grades of gastritis had decreased from 2.00 to 0 and from 2.00 to 1.50 in the antrum and the corpus,
respectively, while the patient turned out to be 

*H pylori* negative.

Five patients (two men, three women, aged 51–65 years, mean 59 (5) years) had a new diagnosis of lymphocytic gastritis at the second examination (fig 1). Three of them had been *H pylori* negative at the first examination, but turned out to be *H pylori* positive at the second one. The appearance of the features of lymphocytic gastritis was associated with significant increases in the grades of corpus gastritis (p = 0.043) and neutrophilic granulocytes in the corpus (p = 0.043) (fig 3). No significant changes emerged in the other indices of gastritis examined (data not given here).

Nine of the 12 patients (75%) with lymphocytic gastritis at the second examination (group LG2) were *H pylori* positive histologically. However, all of the 12 patients had positive titres (a titre $\geq 500$) of specific *H pylori* IgG antibodies. The level of titres was higher in this group (p = 0.017) than in the randomly taken age and sex matched controls with *H pylori* positive gastritis (group non-LG2, three men and nine women aged 52–72 years, mean 60 (7) years) (fig 4). The numbers of *H pylori* in both the antral and the corpus mucosa were higher in non-LG2 patients than in LG2 patients (p = 0.0001 and p = 0.0003, respectively) (table 2). Similarly, the quantities of *H pylori* in both the antral and the corpus mucosa were higher in non-LG1 patients than in LG1 patients (p = 0.004 and p = 0.028, respectively) (table 1). Unfortunately, *H pylori* antibodies could not be determined at the first examination.

The grades of antral gastritis and neutrophilic granulocytes were higher in non-LG2 patients than in LG2 patients (p = 0.016 and p = 0.018, respectively). In contrast, there were higher grades of corpus gastritis (p = 0.009), neutrophilic granulocytes (p = 0.033), eosinophilic granulocytes (p = 0.005), mononuclear leukocytes (p = 0.0002), and foveolar hyperplasia (p = 0.005) in LG2 patients than in non-LG2 patients (table 2). Comparisons of the indices of inflammation between LG1 patients and non-LG1 patients mostly yielded analogous results (table 1).

The lymphocytic gastritis patients had no typical findings at endoscopy. Five of these 12 patients had normal endoscopic findings at the second examination. One patient had undergone a gastric resection because of a gastric ulcer and she had a normal appearing resected stomach. Two patients had a duodenal ulcer scar and four had an endoscopic diagnosis of gastritis. None of the patients had erosions, endoscopic signs of hypertrophic gastropathy, or a clinical diagnosis of coeliac disease. Two patients had used antimicrobial drugs during the past year, but not during the past month. Both of them were *H pylori* positive histologically. One patient was using an antacid daily and she was *H pylori* positive histologically. None of the patients had been treated for *H pylori* during the 10 year follow up.

Table 2. Comparisons of the indices of gastritis and the quantities of *H pylori* in the antral and corpus mucosa in patients with lymphocytic gastritis at the second examination (LG2) and in controls (non-LG2)

<table>
<thead>
<tr>
<th>Antrum</th>
<th>LG2 (n = 12)</th>
<th>Non-LG2 (n = 12)</th>
<th>Statistical significance</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis, grade range</td>
<td>1-00 0.67-2.25</td>
<td>1.88 0.50-2.25</td>
<td>0.016</td>
<td>1.00-3.00 0.00-3.00</td>
</tr>
<tr>
<td>Mononuclear cells, grade range</td>
<td>1.75 1.00-2.75</td>
<td>1.88 0.50-2.75</td>
<td>NS</td>
<td>2.50 1.00-2.00</td>
</tr>
<tr>
<td>Neutrophilic cells, grade range</td>
<td>0.33 0.00-2.00</td>
<td>1.25 0.00-3.00</td>
<td>0.018</td>
<td>1.54 0.05-2.50</td>
</tr>
<tr>
<td>Eosinophilic cells, grade range</td>
<td>0.00 0.00-2.00</td>
<td>0.00 0.00-2.00</td>
<td>NS</td>
<td>1.88 0.00-3.00</td>
</tr>
<tr>
<td>Hyperplasia, grade range</td>
<td>1.00 0.00-2.50</td>
<td>1.00 0.00-1.75</td>
<td>NS</td>
<td>1.71 1.00-2.50</td>
</tr>
<tr>
<td>Metaplasia, grade range</td>
<td>0.00 0.00-0.50</td>
<td>0.25 0.00-1.00</td>
<td>NS</td>
<td>0.00 0.00-2.00</td>
</tr>
<tr>
<td>Numbers of <em>H pylori</em>, score, median range</td>
<td>0.00 0.00-1.75</td>
<td>2.00 0.50-3.00</td>
<td>0.0001</td>
<td>0.50 0.00-2.00</td>
</tr>
</tbody>
</table>
Lymphocytic gastritis

Discussion
Lymphocytic gastritis is a chronic inflammatory process of unknown aetiology and clinical significance. The earlier studies were mostly based on cross sectional data from a limited number of patients.\textsuperscript{1,3,7,11} Prevalences of 4-5% in patients with chronic active gastritis,\textsuperscript{2} 0-83% in patients with dyspepsia,\textsuperscript{14} and 3-7% in children and adolescents\textsuperscript{1} have been reported. We were able to find nine lymphocytic gastritis patients for our follow up study in an endoscopic series of 96 patients with dyspepsia (9%). The prevalence of lymphocytic gastritis may be dependent on the population studied, as is the prevalence of \textit{H. pylori} infection,\textsuperscript{15} and atrophy and intestinal metaplasia of the gastric mucosa.\textsuperscript{16,17} Lymphocytic gastritis is more common among females, and the mean age of lymphocytic gastritis patients is 45-49 years.\textsuperscript{2,14} Thus the present high prevalence might in part be connected with the age and sex distribution of our material. In addition, the numbers of IEL vary in gastric mucosa\textsuperscript{1} - the large number of systematically taken specimens (four antral and four corpus biopsies) in the present study probably increased the yield of lymphocytic gastritis cases. Furthermore, the diagnostic criteria for lymphocytic gastritis used in different studies are not identical and this may have some effect on the number of cases. Criteria based on the maximum concentration of IEL used in the present study\textsuperscript{1} may produce more diagnoses of lymphocytic gastritis than those based on counts of IEL on random fields\textsuperscript{18} or counts based on immunohistochemical staining of T lymphocytes.\textsuperscript{14} The features of lymphocytic gastritis were most commonly detected in corpus mucosa, which is in line with the results of the earlier studies.\textsuperscript{12} The present follow up study might be taken as representing the history of lymphocytic gastritis in late middle and old age. The natural course of the disease may be confounded by antibiotic or other treatments between the first and the second examination, and this bias was eliminated only during the few months preceding the examinations. The small number of patients further limits the value of the conclusions, but the longitudinal design offers some significant results.

It has been suggested that lymphocytic gastritis represents an abnormal response of the gastric mucosa to \textit{H. pylori} infection.\textsuperscript{2} Evidence of \textit{H. pylori} infection has been found in 40% of the gastric biopsies obtained from lymphocytic gastritis patients\textsuperscript{1} and in 82% of serologically tested lymphocytic gastritis patients.\textsuperscript{2} In the latter study, some of the serologically \textit{H. pylori} positive patients (four out of nine) were histologically \textit{H. pylori} negative. In the present study, 75% (9/12) of the lymphocytic gastritis patients were \textit{H. pylori} positive histologically and all were \textit{H. pylori} positive serologically. In addition, the levels of \textit{H. pylori} specific IgG antibodies were significantly higher in the lymphocytic gastritis patients as in the non-lymphocytic gastritis \textit{H. pylori} positive patients. Furthermore, the patients with lymphocytic gastritis had a higher degree of corpus gastritis involving slight to moderate atrophy than the patients with non-lymphocytic \textit{H. pylori} positive gastritis. Three of the five patients who developed lymphocytic gastritis during the follow up turned out to be \textit{H. pylori} positive, and the appearance of lymphocytic gastritis was associated with a significant increase in the activity of corpus gastritis. \textit{H. pylori} usually causes antral or both antral and corpus gastritis,\textsuperscript{23} but our results suggest that some patients develop a gastritis that predominates in the corpus and is associated with an increase in the intraepithelial lymphocyte count. This process may eventually lead to a disappearance of \textit{H. pylori}, while there are still specific antibodies left. It is also possible that the patients with atrophic corpus gastritis show a high prevalence (86%) of seropositivity and a low prevalence of positive histological staining for \textit{H. pylori}.\textsuperscript{20} It is possible that in some cases the \textit{H. pylori} associated lymphocytic gastritis-type corpus gastritis is an intermediate stage in the development of atrophic corpus gastritis and pernicious anaemia.

Although the association between \textit{H. pylori} and lymphocytic gastritis seems strong, it might still be coincidental. However, \textit{H. pylori} is not usually identified in patients with any form of specific gastritis.\textsuperscript{21} The association of lymphocytic gastritis with \textit{H. pylori} gastritis and eosinophil disease suggests that this type of response may be caused by several antigens, one of which is \textit{H. pylori}. It is known that \textit{H. pylori} can stimulate both peripheral blood and mucosal T lymphocytes to proliferate and secrete cytokines.\textsuperscript{22-24} It is probable that the increased number of intraepithelial lymphocytes, as in lymphocytic gastritis, is a particular response associated with the cell mediated immune cascade to \textit{H. pylori}.

The severity of antral\textsuperscript{11,25} and corpus\textsuperscript{25} gastritis has been shown to be positively correlated with the numbers of \textit{H. pylori} in the gastric mucosa. The natural course of the disease may be confounded by antibiotic or other treatments between the first and the second examination, and this bias was eliminated only during the few months preceding the examinations. The small number of patients further limits the value of the conclusions, but the longitudinal design offers some significant results.

Lymphocytic gastritis and dyspepsia,\textsuperscript{14} with the prevalence of \textit{H. pylori} infection being 6-22% in patients with dyspepsia and 78% (7/12) of the cases of the organism could only be found in the corpus mucosa. We have previously shown the numbers of \textit{H. pylori} to be inversely related to intraepithelial lymphocytes.\textsuperscript{25} Hence, there is a trend towards a suppression of \textit{H. pylori} by suppression of treatment. This theory is in line with the results of our study, where the appearance of \textit{H. pylori} and lymphocytic gastritis was associated with an increase in the activity of corpus gastritis. This process may eventually lead to a disappearance of \textit{H. pylori}, while there are still specific antibodies left. It is also possible that the patients with atrophic corpus gastritis show a high prevalence (86%) of seropositivity and a low prevalence of positive histological staining for \textit{H. pylori}.\textsuperscript{20} It is possible that in some cases the \textit{H. pylori} associated lymphocytic gastritis-type corpus gastritis is an intermediate stage in the development of atrophic corpus gastritis and pernicious anaemia.
described. A spontaneous disappearance of \textit{H pylori} infection has been shown to occur in up to 13\% of cases during a follow up for 10 years.\textsuperscript{12,27}

In the present study, the development of gastritis in lymphocytic gastritis patients was only partly comparable with that in patients with non-lymphocytic, \textit{H pylori} positive gastritis. Most notably, the grade of intestinal metaplasia in the corpus appeared to increase in the lymphocytic gastritis patients who simultaneously showed a decline in the numbers of \textit{H pylori} in the corpus and antral mucosa. We were unable to detect similar phenomena in either the non-lymphocytic gastritis \textit{H pylori} positive patients used here as controls or in the patients included in the recent follow up studies on \textit{H pylori} positive gastritis\textsuperscript{23} and gastric ulcer.\textsuperscript{26}

It has been suggested that the progression of intestinal metaplasia creates a hostile environment for \textit{H pylori}.\textsuperscript{29} According to the present results, the progression of intestinal metaplasia in the corpus mucosa is more typical of lymphocytic gastritis than non-lymphocytic, \textit{H pylori} positive gastritis. Documentation of changes in patchy lesions, such as intestinal metaplasia, is difficult even when multiple biopsies are used, as here. Studies on larger patient series are needed to determine whether lymphocytic gastritis or other factors may promote the progression of intestinal metaplasia. Intestinal metaplasia has been proposed to be a precursor of gastric carcinoma,\textsuperscript{30} which underlines the importance of studying the behaviour of this lesion. Interestingly, in a recent study it was reported that lymphocytic gastritis was associated with gastric adenocarcinoma and primary gastric lymphoma.\textsuperscript{31}

In conclusion, the features of lymphocytic gastritis in gastric mucosa are usually persistent. Most of our lymphocytic gastritis patients were \textit{H pylori} positive histologically and all were serologically \textit{H pylori} positive. The results suggest that \textit{H pylori} occasionally causes a gastritis that predominates in the corpus and is reflected as an increase of the intraepithelial lymphocyte count. Lymphocytic gastritis-type gastritis may promote the progression of intestinal metaplasia and gastritis in the corpus mucosa.