Lymphocytic gastritis and *Helicobacter pylori* infection in gastric lymphoma

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Abstract

Lymphocytic gastritis and primary gastric lymphoma are rare conditions with unknown aetiology. It has recently been suggested that *Helicobacter pylori* has a role in the pathogenesis of both of them. The occurrence of lymphocytic gastritis and *H pylori* was studied in a series of patients with primary gastric lymphoma. The cases of primary gastric lymphomas (n=35) diagnosed in years 1970-1993 were identified. The specimens of 22 cases contained gastric mucosa sufficiently so that the number of intraepithelial lymphocytes, severity of gastritis, and occurrence of *H pylori* could be studied. Lymphocytic gastritis was detected in seven of 22 patients (32%), and in most cases both in antral and body mucosa. Atrophy of the body glands was significantly more severe in lymphocytic gastritis patients. *H pylori* was detected in 13 of all 22 patients (59%); two of seven lymphocytic gastritis patients (29%), and 11 of 15 (73%) of patients without lymphocytic gastritis were *H pylori* positive. Patients with gastric lymphoma have significantly increased prevalence of lymphocytic gastritis. Rarity of *H pylori* in these patients might be connected with atrophic changes in body mucosa. Further studies are needed to show the significance of lymphocytic gastritis as a precursor of gastric lymphoma.

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Keywords: gastric lymphoma, *Helicobacter pylori*, lymphocytic gastritis, intraepithelial lymphocyte.

A process characterised by a heavy increase in intraepithelial lymphocytes in gastric mucosa was first described in 1985 by Haot *et al*¹ and Rubio *et al*² and later termed lymphocytic gastritis. The frequency of lymphocytic gastritis among unselected endoscopy patients has varied from 0.8% to 4.5%³⁻⁵; lymphocytic gastritis is more common in coeliac disease.⁶ Significance of lymphocytic gastritis and aetiology are unknown, but abnormal reaction to some nutritional antigen or *Helicobacter pylori* has been suggested.³

Primary lymphoma of the gastric mucosa is a rare disease representing 1 to 5% of gastric malignancies,⁷⁻⁹ but the incidence is increasing.^{10,11} Most gastric lymphomas arise from mucosa associated lymphatic tissue,¹² but their aetiology is otherwise obscure. Recently Wotherspoon *et al*¹³ detected *H pylori* infection in 92% of cases with gastric lymphoma and

suggested that the infection may have a role in the pathogenesis of lymphoma.

As intraepithelial lymphocytes are speculated to have a role in the regulation of normal mucosal inflammatory reaction^{14,15} they may also participate in the pathogenesis of mucosal lymphoma, where abnormal antigen stimulation or abnormal regulation of the immune response is suspected to play an important part.¹⁶ Recently we saw a case of primary gastric lymphoma of B-cell type associated with *H pylori* infection and heavy increase of intraepithelial T-lymphocytes fulfilling the criteria of lymphocytic gastritis. This finding prompted us to study a series of primary gastric lymphomas and evaluate the occurrence of lymphocytic gastritis and *H pylori* infection. Clinical features and characteristics of gastric mucosa were analysed to understand the potential connection between lymphocytic gastritis and gastric lymphoma.

Methods

Patients

The study consisted of all patients diagnosed with primary gastric lymphoma in years 1970-1993 in the department of pathology, University of Oulu. Gastric lymphomas were regarded primary if the stomach was the only or most massively affected organ; no peripheral or mediastinal lymphadenopathy was present at the early stage of lymphoma and the leucocyte number in blood was within normal range.¹⁷

Classification and staging of tumours

The histological diagnosis was based on 4 µm sections made from original formalin fixed, paraffin wax embedded specimens stained with haematoxylin and eosin. Additional sections were stained with L26 antibody (CD20; Dako, Copenhagen, Denmark) and UCHL1 (CD45RO); Dako, Copenhagen, Denmark), to verify cell lineage of tumour and intraepithelial lymphocytes.

Gastric lymphomas were typed according to the classification used by Isaacson *et al*.¹⁸ For staging, a modified Ann Arbor system was used.¹⁹⁻²¹

Information of clinical history and the localisation, size, and macroscopic appearance of lymphoma were collected from the patient records. Because the exact size of the tumours was mostly unknown, the cases were classified in three categories according to the approximate largest diameter: (a) small, diameter 1 cm or less; (b) middle sized, diameter 1 to 3 cm; and (c) large, diameter 3 cm or more.

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TABLE I Histological typing of gastric lymphomas in patients with and without lymphocytic gastritis (LG). 'Unknown' category includes 13 cases where histological specimens did not represent gastric mucosa

Lymphoma type	LG	No LG	Unknown
Low grade B cell lymphoma	3	8	8
High grade B cell lymphoma	4	6	5
Low grade T cell lymphoma	0	1	0

Estimation of intraepithelial lymphocyte numbers and diagnosis of lymphocytic gastritis

In each case the numbers of intraepithelial lymphocytes were estimated separately in antral mucosa, body mucosa, and near tumour using haematoxylin and eosin stained sections. Thickness of section may affect the assessment of objects of different sizes²² such as intraepithelial lymphocytes and epithelial cells. Therefore the uniformity of thickness was first verified by measuring section thickness with modified Small's method.²² Areas close to the tumour were avoided when counting antral and body intraepithelial lymphocytes and measurement was done at least 5 mm from the lateral margin of the tumour. In most cases the distance from the tumour was more than 1 cm. Counting for areas close to the tumour was performed in surface and foveolar epithelium immediately above the tumour avoiding regions with erosions or direct epithelial infiltration of tumour cells. In each of the three regions 100 consecutive cells of surface and foveolar epithelium were counted in three randomly selected areas of surface and foveolar epithelium using haematoxylin and eosin stained sections. Lymphocytes forming lymphoepithelial lesions²³ close to germinal centres or lymphoma infiltrate could be easily recognised and were not counted. Exclusion of cells forming lymphoepithelial lesions was based on several features. Intraepithelial lymphocytes were surrounded by a clear halo. Their nuclei were smaller and more roundish than in lymphocytes of lymphoepithelial lesions. Lymphocytes of lymphoepithelial lesions often formed groups of several cells while intraepithelial lymphocytes stayed mostly as single cells and were evenly distributed in foveolar and surface epithelium. Three counts from each area were pooled, and

expressed as intraepithelial lymphocytes per 100 epithelial cells. As some cases with moderate diffuse increase of intraepithelial lymphocytes (25–30 intraepithelial lymphocyte/100 epithelial cells) showed heavy increase focally, the number of intraepithelial lymphocytes was additionally counted in the most affected areas.

Lymphocytic gastritis was diagnosed if the count of intraepithelial lymphocytes in antral or body mucosa distant to the area of lymphoma was >30/100 epithelial cells.²⁴

Estimation of severity of gastritis and occurrence of *H pylori*

The severity of gastritis in antral and body mucosa was estimated by using a five point scale²⁵ from normal (grade 0), to superficial gastritis (grade 1); slight, moderate, and severe atrophic gastritis (grades 2, 3, and 4). The extent of intestinal metaplasia, the numbers of mononuclear inflammatory cells in lamina propria, neutrophilic leucocytes, and eosinophilic leucocytes were estimated in grades showing a spectrum from the normal state (grade 0) to slight (1), moderate (2), and heavy (3) increase.²⁵ These gradations are closely comparable with those of the Sydney system.²⁶

The presence of *H pylori* was first studied using haematoxylin and eosin stained sections of antral and body mucosa. Cases negative in haematoxylin and eosin stainings were further analysed using the modified Giemsa staining. The quantity of *H pylori* was graded according to Marshall *et al*²⁷ using a four point scale from absent (grade 0) to abundant (grade 3).

Results

Patients and histological types of primary gastric lymphomas

There were 35 patients (63 median age, 27–85 range) with primary gastric lymphoma consisting of 15 women (65 median age, 28–79 range) and 20 men (56 median age, 27–85 range). Table I shows the distribution of lymphoma types. Immunohistochemical stainings showed in 33 cases features of B cell lymphomas (L26 positivity, UCHL1 negativity). One case was positive for UCHL1 and negative for L26 and was classified as a small cell pleomorphic type of T cell lymphoma. In one case material available for immunohistochemical stainings did not contain tumour tissue, and the case was classified as immunoblastic high grade type of B cell lymphoma according to haematoxylin and eosin staining.

The specimens of 13 patients represented neither antral or body mucosa; in these cases the presence or absence of gastritis or *H pylori* could not be evaluated and these patients were excluded from the analysis. The samples of 22 patients were included; in 14 patients both antral and body mucosa outside lymphoma could be evaluated, in two patients only antral and in six patients only body mucosa could be studied.

Figure 1: Number of intraepithelial lymphocytes in antrum and body in lymphoma patients with and without lymphocytic gastritis (LG).

Figure 2: (A) Lymphocytic gastritis in association with gastric lymphoma. Most of the intraepithelial lymphocytes are UCHL1 positive (arrowheads). UCHL1, magnification $\times 384$. (B) Lymphoma cells are not stained with UCHL1 (arrows). Same case as in (A). UCHL1, magnification $\times 384$.

Intraepithelial lymphocyte counts and occurrence of lymphocytic gastritis

There were seven of 22 patients (32%) fulfilling the criteria of lymphocytic gastritis.²⁴ In five of them a heavy diffuse increase of intraepithelial lymphocytes was present, as shown by occurrence of >30 intraepithelial lymphocytes in non-selected areas of antral or body mucosa. In two patients a moderate increase of intraepithelial lymphocytes (25–30/100) in random areas was accompanied with a heavy increase ($>30/100$) in the most affected area of antral or body mucosa. All seven cases represented B cell lymphomas. Measured thickness of sections were similar both in patients with lymphocytic gastritis (mean (SD) $4.82 \mu\text{m}$ (0.43); range 4.0–5.25) and without lymphocytic gastritis ($4.88 \mu\text{m}$ (0.33); 4.25–5.25).

Usually the number of intraepithelial lymphocytes was roughly the same in all areas of the mucosa including the vicinity of the tumour. The number of intraepithelial lymphocytes in the antrum correlated with those in the body (Spearman rank correlation 0.534, $p=0.001$) and in the tumour area (Spearman 0.366, $p=0.05$). Figure 1 shows the distribution of

intraepithelial lymphocyte counts in non-selected areas of antral and body mucosa in patients with and without lymphocytic gastritis. The median number of intraepithelial lymphocytes close to the tumour was 34 (range 25–50) in patients with lymphocytic gastritis and 11 (8–22) without lymphocytic gastritis.

About 40–70% of intraepithelial lymphocytes were positive for UCHL1 (Fig 2A and B), while none of them were positive for L26 (Fig 3). Cells forming lymphoepithelial lesions were negative for UCHL1 and positive for L26.

No significant differences in size, stage or localisation of tumours with and without lymphocytic gastritis were seen (Tables II and III). Age and sex distribution and occurrence of other diseases were similar in patients with and without lymphocytic gastritis (Table IV).

Severity of gastritis and occurrence of H pylori infection

Gastritis was present in all patients. There were no significant differences in the numbers of eosinophilic granulocytes, lamina propria mononuclear inflammatory cells or intestinal metaplasia between patients with and without lymphocytic gastritis. There were more neutrophilic granulocytes in antral mucosa in patients with lymphocytic gastritis (median score 1.5; range 1–2) than in patients without lymphocytic gastritis (median 1; range 0–2; $p=0.04$, Mann-Whitney test). In addition, more advanced body atrophy was present in patients with lymphocytic gastritis (median score 2; range 2–3) than in patients without lymphocytic gastritis (median 1; range 1–3; $p=0.01$; Figs 4 and 5). Association of intraepithelial lymphocyte numbers and severity of gastritis was also evident from correlation between body intraepithelial lymphocyte count and body gastritis (Spearman r 0.452, $p=0.01$), intestinal metaplasia (r 0.435, $p=0.01$), and mononuclear inflammatory cells in body mucosa (r 0.361, $p=0.05$).

Figure 3: Lymphocytic gastritis in association with gastric lymphoma; same case as in Fig 2(A) and (B). Lymphoma infiltration is L26 positive (arrows), but none of intraepithelial lymphocytes are stained (arrowheads). L26, magnification $\times 384$.

TABLE II Staging of gastric lymphomas in patients with and without lymphocytic gastritis (LG). 'Unknown' category includes cases where histological specimens did not represent gastric mucosa

Lymphoma stage	LG	No LG	Unknown	Total
EI 1	1	3	3	7
EI 2	3	7	2	12
EII 1	0	2	2	4
EII 2	0	0	0	0
EIII	0	0	0	0
EIV	2	2	0	4
Stage unknown	1	1	6	35

EI 1, lymphoma confined to mucosa or submucosa. EI 2, lymphoma extending beyond submucosa. EII 1, regional lymph nodes involved. EII 2, lymph nodes involved beyond regional area. EIII, involved areas on both sides of diaphragm. EIV, non-gastrointestinal organs involved.

H. pylori could be found in 13 of 22 patients (59%). There were two *H. pylori* positive cases among patients with lymphocytic gastritis (29%) and 11 among patients without (73%) ($p=0.056$, Fisher's test). Figure 5 shows *H. pylori* status and the degree of body gastritis in cases in which both of them could be evaluated ($n=20$). The number of *H. pylori* organisms was small in all patients (median score in patients with lymphocytic gastritis 0, range 0–1; median score in patients without lymphocytic gastritis 1, range 0–2; non-significant). The number of intraepithelial lymphocytes in body mucosa was significantly higher in *H. pylori* negative patients (26 median, 9–33 range) than in *H. pylori* positive ones (10 median, 4–35 range; $p=0.048$, Mann-Whitney). The other clinical or histological parameters did not differ significantly between *H. pylori* positive and negative patients.

Discussion

Our retrospective study showed that lymphocytic gastritis is common in patients with primary gastric lymphoma. The frequency (32%) is clearly higher than that reported in non-ulcer dyspepsia (0.8–2.4%)^{3,4} and chronic active gastritis (1.6–4.5%).⁴ Furthermore the number of intraepithelial lymphocytes (mean 11.9 in antrum and 10.1 in body) in lymphoma patients without lymphocytic gastritis was also higher than the reference values given for dyspepsia patients (3.7/100)³ and for patients with histologically normal mucosa (2.5/100).²⁸

Intraepithelial lymphocytes were easily recognised in haematoxylin and eosin stained sections because of the so-called 'halo' surrounding them and their smaller nuclei compared with epithelial cells. The increase of intraepithelial lymphocytes in lymphocytic

TABLE III Localisation of lymphomas in patients with and without lymphocytic gastritis (LG). 'Unknown' category includes cases where histological specimens did not represent gastric mucosa

Lymphoma localisation	LG	No LG	Unknown
Oesophagus and cardia	0	0	0
Cardia	0	0	2
Cardia and corpus	0	3	2
Corpus	2	3	5
Corpus and antrum	3	3	1
Antrum	0	4	0
Antrum and pylorus	1	2	0
Several regions	1	0	0
Unknown	0	0	3

TABLE IV Clinical features of lymphoma patients with and without lymphocytic gastritis (LG). No significant differences between the groups could be seen

	LG	No LG
Median age (range)	58 (36–72)	64 (27–85)
Mean age (SD)	57.1 (11.0)	61.1 (18.1)
Males/females	3/4	8/7
Accompanying diseases		
Diabetes (type II)	1	1
Rheumatoid arthritis	1	1
Tuberculosis	0	1

gastritis was most diffuse in surface and foveolar epithelium and was present both in antral and body mucosa as well as mucosa in the vicinity of the tumour. Lymphoepithelial lesions, which are present in mucosa associated tissue lymphomas²³ were clearly different in appearance and location and could be distinguished from intraepithelial lymphocytes. Intraepithelial lymphocytes were smaller than the cells of lymphoepithelial lesions. They were evenly distributed and mostly occurred as single cells in contrast with cells of lymphoepithelial lesions, which are rather tight clusters of several cells. This discrimination between intraepithelial lymphocytes and cells of lymphoepithelial lesions was supported by the findings of immunohistochemical stainings. Most but not all intraepithelial lymphocytes stained positively with a T cell antibody used (anti-CD45RO) and did not stain, in contrast with the tumour cells, with a B cell antibody L26. This shows that intraepithelial lymphocytes, being T lymphocytes,^{14,29} are not of the same cell lineage as the lymphoma cells.

Mechanisms for the increase in the number of intraepithelial lymphocytes and occurrence of lymphocytic gastritis in gastric lymphomas remain unclear. Recently, nodal B cell lymphomas with heavy increase of reactive T cells have been described.³⁰ The possibility that intraepithelial lymphocytes in our cases of gastric lymphomas represent overflow of tumour associated T lymphocytes seems an unlikely explanation: the excess of intraepithelial lymphocytes was present both in the proximity of lymphoma and on areas distant from the tumour, both in antral and body mucosa. Furthermore, no correlation between the size or stage of the tumour and the number of

Figure 4: Lymphocytic gastritis in body. Note moderate loss of glands; inset shows intraepithelial lymphocytes. Haematoxylin and eosin, magnification $\times 26$; inset, magnification $\times 128$.

Figure 5: Grade of body gastritis and *H. pylori* status in patients with and without lymphocytic gastritis (LG). *H. pylori* positive cases are shown as solid circles and *H. pylori* negative cases as open circles.

intraepithelial lymphocytes was seen suggesting that increase of intraepithelial lymphocytes is not secondary to tumour growth. In gastric lymphomas, however, cells of the neoplastic clone may be present outside the main tumour mass among reactive inflammatory cells,³¹ and the possibility that lymphoma cells have some role in the development of lymphocytic gastritis cannot be totally excluded.

Gastric lymphoma, like other lymphomas of mucosa associated lymphatic tissue, are considered to develop against the background of chronic inflammation.^{13 32 33} Recently Wotherspoon *et al*¹³ and Doglioni *et al*³⁴ showed an association between *H. pylori* associated gastritis and gastric lymphoma; in 87–92% of the cases *H. pylori* could be detected in histological sections. In our study gastritis was present always supporting the concept of inflammation as an important background condition for gastric lymphoma, but *H. pylori* status showed an interesting pattern among patients with lymphocytic gastritis. *H. pylori* was remarkably rare among lymphoma patients with lymphocytic gastritis, only 29% (two of seven) being *H. pylori* positive, whereas 73% (11 of 15) of lymphoma cases without lymphocytic gastritis were *H. pylori* positive. Rarity of actual *H. pylori* infection in lymphoma patients with lymphocytic gastritis might be connected with more pronounced atrophic changes in body mucosa in them. Quantity of *H. pylori* in infected patients is inversely related to acid secretory capacity of body mucosa²⁵ and serological evidence of *H. pylori* infection is common in patients with atrophic gastritis in the body while the bacterium itself is not detectable.³⁵ Accordingly, it is possible that our *H. pylori* negative cases have been previously positive but the bacterium has disappeared together with the impairment of acid secretion from the body mucosa. No direct evidence for this assumption in this study is available as no previous biopsy specimens or serum samples were available. Interestingly, *H. pylori* is only rarely detected histologically in lymphocytic gastritis, although strong serological response is common.³

Potential common mechanisms for the simultaneous occurrence of lymphocytic gastritis and atrophy of body glands in lymphoma patients remain entirely speculative. Although

intraepithelial lymphocytes are probably heterogeneous in function,¹⁴ in lymphocytic gastritis they are mostly CD8 positive cells (cytotoxic/suppressor T-cells)³⁶ and may play a part in negative regulation of immune response. Thus an increased amount of intraepithelial lymphocytes might be a reaction to abnormal antigen or an indication of abnormal regulatory mechanism of the host.

Chronic gastritis is a well known precursor of gastric cancer and cross sectional studies of cancerous stomachs have shown that the severity of the risk is related to the degree of glandular atrophy.³⁷ For gastric lymphomas, no risk indicators of this importance are known. We suggest that lymphocytic gastritis may be a potential risk factor for gastric lymphoma. Differences in the reported mean ages in lymphocytic gastritis and lymphoma support this hypothesis; mean age of lymphocytic gastritis (46.5–48.8 years)^{3 4 38} is less than that seen for our lymphoma patients with lymphocytic gastritis (57.1 years), or average age of gastric lymphoma in other reports (58–62 years).^{34 39}

In summary, increase in the number of intraepithelial lymphocytes and lymphocytic gastritis is common in primary gastric lymphoma. Furthermore lymphocytic gastritis was associated with more advanced body gastritis. The reason for the rarity of *H. pylori* in the lymphoma patients with lymphocytic gastritis compared with other lymphoma patients is not known but it may be related to the atrophic changes in the body mucosa. Further studies are needed to find out whether lymphocytic gastritis is a precursor state for gastric lymphoma.

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