

Lymphoid follicles in antral mucosa: immune response to *Campylobacter pylori*?

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SUMMARY The prevalence of lymphoid follicles in endoscopic biopsy specimens from normal antral mucosa (n = 220), mucosa with reflux gastritis (n = 104), and in cases with *Campylobacter pylori*-associated gastritis (n = 2544) was studied. In the latter group whether there were associations between degree and activity of gastritis and the prevalence of lymphoid follicles and between the occurrence of lymphoid follicles and the presence of intestinal metaplasia in the antrum were investigated. In cases with normal mucosa and in those with reflux gastritis lymphoid follicles were not detected, but mucosal lymphoid follicles were found in 1297 (54%) of the cases with *C pylori*-associated gastritis. The prevalence of lymphoid follicles in the antral mucosa depended on the degree and activity of the gastritis and also correlated with the presence of intestinal metaplasia.

The development of lymphoid follicles in the mucosa of the antrum probably represents, primarily, an immune response to the colonisation of the mucosa by *C pylori*.

While lymphoid follicles in the small intestine and colon are characteristic of a normal gastrointestinal tract,^{1,2} they are completely absent from the healthy stomach.¹⁻⁴ Although their presence in the stomach in gastritis^{3,5} or in the marginal areas of lymphomas⁶⁻⁸ has been repeatedly described both endoscopically and histologically, their pathogenesis is still unclear. In 1988 Wyatt and Rathbone⁹ and our own working group¹⁰ showed for the first time that hyperplasia of the lymphoid follicles apparently represents at least part of the response for *Campylobacter pylori*-associated gastritis.

This study aimed at determining how often lymphoid follicle hyperplasia occurs in *C pylori*-associated antral gastritis, and whether these follicles can also be detected in normal antral mucosa and in reflux gastritis. Whether the prevalence of lymphoid follicles depends on the degree of lymphoplasmocellular infiltration or the activity of *C pylori*-associated gastritis, or both, and whether there is any correlation with intestinal metaplasia were also investigated.

Material and methods

Forceps biopsy specimens obtained from the antrum (at least two from each patient), stained with

haematoxylin and Warthin-Starry in three groups of patients with the following histological diagnoses were investigated. Group 1: antral mucosa showing no pathological changes (n = 220); group 2: antral mucosa with the typical appearance of reflux gastritis (n = 104); group 3: antral mucosa with the typical appearance of *C pylori*-associated gastritis (n = 2544).

Antral mucosa was defined as that showing no pathological changes when a normally structured mucosa with no evidence of infiltration by lymphocytes, plasma cells or polymorphonuclear leucocytes was found. Reflux gastritis was diagnosed in accordance with the criteria proposed by Dixon *et al.*¹¹ Detection of *C pylori* prompted the diagnosis of *C pylori*-associated gastritis. In this type of gastritis the degree of colonisation of antral mucosa by the organism, the degree of chronic gastritis, measured by the density of infiltration of the lamina propria by lymphocytes and plasma cells, and the degree of activity, measured by the density of infiltration with neutrophils, were assessed semiquantitatively in accordance with the criteria shown in the table. In the case of *C pylori*-associated gastritis an attempt was made to establish whether the occurrence of lymphoid follicles correlated with the presence of intestinal metaplasia. The two main forms of intestinal metaplasia (incomplete and complete) were "pooled".

Statistical analysis was performed by the χ^2 test.

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Table Degree and activity of gastritis and *Campylobacter pylori* colonisation

		Degree of gastritis	Activity of gastritis	<i>C pylori</i> colonisation
I	Minimal	Only very occasional, uniformly distributed lymphocytes and plasma cells in the upper lamina propria	Occasional neutrophils demonstrable in the lamina propria	Only minimal, focal <i>C pylori</i>
II	Low grade	Uniform "loose" infiltration of the upper lamina propria by lymphocytes and plasma cells	Few neutrophils in the lamina propria with no leucopedesis in the region of the gastric pits	Few, uniformly distributed <i>C pylori</i>
III	Medium grade	Moderately dense infiltration of the upper lamina propria by lymphocytes and plasma cells	Moderate numbers of neutrophils in the lamina propria with moderate leucopedesis in the region of the gastric pits	Moderately dense colonisation
IV	High grade	Very dense lymphoplasmocellular infiltration of the lamina propria	Abundant neutrophils in the lamina propria with pronounced leucopedesis and formation of leucocyte "plugs" in the pits	Very dense <i>C pylori</i> colonisation

Results

In normal antral mucosa and in reflux gastritis antral mucosa (groups 1 and 2) lymphoid follicle hyperplasia was not seen. In *C pylori*-associated gastritis, however, group 3, lymphoid follicle hyperplasia was detected in 1297 (54%) of the cases.

The age distribution in the three groups shows that patients with normal antral mucosa or reflux gastritis were significantly younger than those with *C pylori*-associated gastritis (figure). In group 3, overall, however, there was no significant difference between the number of patients with and those without lymphoid follicles.

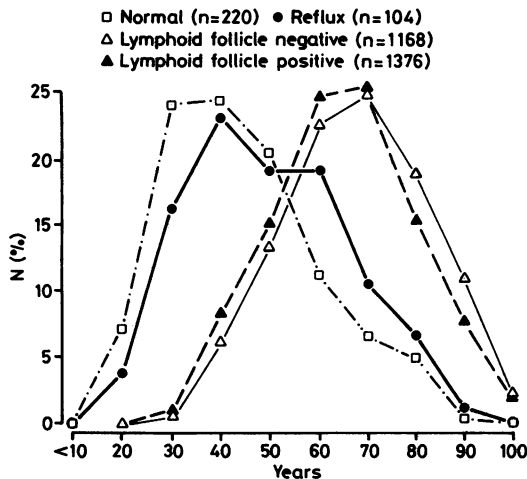


Figure Distribution of cases with normal antral mucosa ("normal"), reflux gastritis, *Campylobacter*-associated gastritis with no lymphoid follicle hyperplasia and *Campylobacter*-associated gastritis with lymphoid follicle hyperplasia.

An analysis of the prevalence of the lymphoid follicles in the antrum as a function of the degree of the *C pylori*-associated gastritis showed that with only minimal lymphoplasmocellular infiltration in the antral mucosa (but only four cases) no lymphoid follicles were found; in mild gastritis lymphoid follicles were seen in 21 of 103 (22%) cases, in moderate gastritis in 948 of 1738 (53%) cases, and in severe gastritis in 403 of 654 (62%) cases. This correlation between the occurrence of lymphoid follicles and degree of lymphoplasmocellular infiltration of the lamina propria of the antral mucosa was highly significant, with a probability of error of less than 0.001.

The prevalence of lymphoid follicles in the antrum also correlated significantly with the activity of gastritis ($p < 0.001$). In the absence of neutrophil infiltration lymphoid follicles were found in only eight of 93 (8.6%), in cases with minimal infiltration in 27 of 82 (33%), those with mild infiltration in 219 of 538 (41%), and in those with moderate infiltration in 870 of 1372 (63%), while the prevalence of lymphoid follicles in high grade activity gastritis again decreases somewhat to 251 of 459 (55%).

When intestinal metaplasia was present in the antrum, lymphoid follicles were found in 334 of 532 (63%) of these cases compared with 1042 of 2012 (52%) of those with antral mucosa and no intestinal metaplasia. This difference was significant ($p < 0.001$).

Discussion

In 1988 Wyatt and Rathbone pointed out that lymphoid follicles represent a relatively common feature of the histological picture of *C pylori*-associated gastritis.⁹ Before that, lymphoid follicles in the gastric mucosa had been represented endoscopically and histologically in a purely descriptive

manner,^{5,12} with nothing being known about their pathogenesis. Prominent lymphoid follicle hyperplasia was designated lymphofollicular gastritis⁶ or pseudolymphoma.^{6,17} Other authors recognised the relation of the antral mucosa to gastritis, which they termed atrophic—without defining whether this really meant total atrophy of the antral mucosal glands.¹³ In this study, which was concerned with the difficult differential diagnosis between “pseudolymphoma” and malignant non-Hodgkin’s lymphoma, the nature of the inflammatory infiltrates was not described, nor was anything said about colonisation by *C. pylori*. The high prevalence of lymphoid follicle hyperplasia of the antral mucosa described earlier by Wyatt and Rathbone⁹ is apparently often detectable in *C. pylori*-associated gastritis. This is shown by our comparison between a group of normal subjects and a group of patients with reflux gastritis. No lymphoid follicle hyperplasia was detected in these two groups, while in *C. pylori*-associated gastritis, it was present in 55% of the cases.

Analysis of the prevalence of lymphoid follicles as a function of the degree of gastritis showed a significant correlation: the more pronounced the gastritis, the more often was lymphoid follicle hyperplasia found. As the degree of gastritis depends on the severity of *C. pylori* colonisation of the mucosa,^{14,15} there is a direct relation, therefore, between the degree of *C. pylori* colonisation and the prevalence of lymphoid follicles in the antrum.

Lymphoid follicle hyperplasia was also correlated with the activity of the gastritis, which itself depends on the degree of colonisation by *C. pylori*.¹⁴ Surprisingly, the prevalence of lymphoid follicles associated with moderate neutrophil infiltration of the lamina propria was much greater than in massive neutrophil infiltration. This finding may be because in the group with gastritis and a pronounced polymorphocellular granulocytic component, colonisation of the gastric mucosa by *C. pylori* had been of a relatively short duration, so that lymphoid follicles had not had time to develop. Lymphoid follicles were detected more often in patients with intestinal metaplasia than in those without metaplastic changes. This may testify to the fact that the formation of lymphoid follicles is a consequence of relatively long standing *C. pylori*-associated gastritis. Although the intestinal metaplastic mucosa itself is not colonised by *C. pylori*, this change is often only focal and the surrounding gastric epithelium shows infestation by the organism. In these cases a possible interpretation for the metaplastic foci could be previous transformation of these areas by an inflammatory process induced by *C. pylori*.

Overall, however, there was no difference in age distribution between the group of patients with *C. pylori*-associated antral gastritis with lymphoid

follicle hyperplasia and those without. This, however, does not provide any indication as to the duration of *C. pylori*-associated gastritis. Although further immunohistochemical studies are still required, our results do seem to show quite clearly that the development of lymphoid follicles in the gastric mucosa is, in the first instance, probably an immune response to the colonisation of the mucosa by *C. pylori*.

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