

Lymphocytic gastritis – prospective study of its relationship with varioliform gastritis

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Abstract

Lymphocytic gastritis is a new histopathological entity characterised by a dense lymphocytic infiltration of surface and pit gastric epithelium. Previous retrospective work has suggested that lymphocytic gastritis is related to an endoscopic form of gastropathy comprising enlarged folds, nodules and erosions, commonly denoted as varioliform gastritis. In the present prospective study, the relationship is clearly shown; nearly 82% (54/66) of the varioliform gastritis observed in four different endoscopy units correspond histologically to lymphocytic gastritis. The correlation is even better if cases showing strictly antral localisation are excluded (53/55) – that is, more than 96%. The histological concept of lymphocytic gastritis seems, however, to extend beyond varioliform gastritis as of 67 cases of lymphocytic gastritis diagnosed during the period under study, one third had no particular endoscopic expression.

In 1947, Moutier and Martin¹ reported two cases of a distinctive inflammatory gastric disease showing widespread mucosal nodules with or without central depressions or erosions associated with an enlargement of the corporeal folds. The name varioliform gastritis is now widely used in the continental scientific literature. Since then, similar endoscopic and radiological features have been described under various names such as aphthous ulcers, chronic erosive gastritis, and 'octopus sucker' gastritis.²⁻⁴

More recently, Lambert *et al*⁵ reporting a series of 90 cases, redefined the entity and distinguished between two forms of varioliform gastritis: one involving the whole stomach was called diffuse varioliform gastritis while the other, being restricted to the antrum, was named antral varioliform gastritis.

In 1985, we identified a new histopathological entity, characterised by dense intra-epithelial lymphocytic infiltration, called lymphocytic gastritis.⁶ Clinicopathological studies have shown that lymphocytic gastritis corresponded, in one third of cases, to a clinical presentation of weight loss and anorexia. Endoscopically lymphocytic gastritis correlated with the finding of nodules, thickened folds and erosions predominating in the corporeal region of the stomach.⁷⁻⁹ All these features appeared to correspond to varioliform gastritis. We have shown in two recent retrospective studies, that the majority of cases diagnosed in the clinical reports as varioliform gastritis revealed on histological examination the typical dense intra-epithelial lymphocytic infiltration of lymphocytic gastritis.^{10 11}

Taking into account, however, the often incomplete and imprecise descriptions in the endoscopic records, as early as 1985, a prospective work was planned with the aim of better defining the correlation between the endoscopic diagnosis of varioliform gastritis and the histological diagnosis of lymphocytic gastritis. The results of this research are presented here.

Methods

The present research was planned by the three endoscopists and two pathologists taking part in the study who agreed on the methodology required to permit valid comparisons between the entities of varioliform gastritis and lymphocytic gastritis. These entities were defined as follows.

The endoscopic features of varioliform gastritis are enlarged and thickened rugal folds bearing erosions and widespread small nodules frequently surmounted by small rounded erosions (aphthoid nodules). According to the topography of the lesions, three forms of varioliform gastritis can be distinguished: diffuse when the whole stomach is involved, corporeal when the anomalies are limited to the body and antral when they are only present in the antrum.

Histologically the diagnosis of lymphocytic gastritis rests upon the presence of an unusually high number of intraepithelial lymphocytes and does not take into consideration other microscopic features often present such as lymphoplasmocytic or neutrophilic infiltrate of the lamina propria.

ENDOSCOPY

In order to permit comparison between endoscopic and histological data a rigorous procedure was followed. All the patients (4840) endoscoped and biopsied between 1985 and 1987 for a non-neoplastic condition of the stomach in four gastroenterology departments (Clinique Notre Dame de Frameries, IMC Peruwelz, Hôpital de Leuze, IMC Beloeil) were included in the study. The endoscopic protocol covered all the anomalies of the gastric mucosa, their number and topography.

HISTOLOGY

In all patients, three to five biopsy specimens were taken from the body as well as from the antrum sampling nodules or erosions and apparently uninvolved mucosa. They were fixed in Bouin's solution and embedded in paraffin. Five micron sections cut made and stained with haematoxylin and eosin.

The two pathologists jointly studied all the

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gastric biopsies originating from the four centres. Without considering the clinical data, they systematically screened the biopsies in search of cases of lymphocytic gastritis. Biopsies were categorised of lymphocytic *versus* other types of gastritis.

As already stated, the diagnosis of lymphocytic gastritis was based on the (subjective) observation of high densities of intraepithelial lymphocytes. Counts were made on all the cases. In order to avoid a bias due to a possible patchiness of distribution, two different biopsy specimens from each patient were read at random. The lymphocytes were counted on an uninterrupted length of 200 surface epithelial cells. The results of the two counts were pooled. A comparison was made with an equivalent number of control cases of chronic atrophic gastritis studied under the same conditions. The cases were chosen from the pool of patients seen in the present series. The controls were paired with each case of lymphocytic gastritis – that is, we chose from our files the first case of chronic atrophic gastritis after a case of lymphocytic gastritis.

Counts were also made on 20 cases where the gastric biopsies were considered histologically normal.

Results

ENDOSCOPIC DATA

Endoscopic diagnosis

Among the 4840 patients examined, 66 (1.4%) were diagnosed as varioliform gastritis. Thirty five were classified as diffuse varioliform gastritis (the sex ratio was 25 men/10 women – average age 44 years; range: 16–82). Twenty were considered as corporeal varioliform gastritis (15 men/five women – average age 47 years; range:

31–82), finally 11 were antral varioliform gastritis: six men/five women – average age 45 years; range: 27–64).

So far as diffuse varioliform gastritis is concerned, the features were consistent. Practically all cases exhibited irregularly thickened folds persisting after distension with air. These extended through the whole body region, thinning progressively down towards the antrum; and were covered by a thick mucus secretion, crossed by large whitish serpiginous erosions lined with fibrin and punctuated at their top by ulcerated nodules (aphthoid nodules) arranged in a stringlike fashion. Flat erosions outside the nodules were rather scarce; they were most often seen in the antral region.

The picture of corporeal and antral varioliform gastritis was, as a whole, characteristic but less pronounced than in the diffuse form. The folds were less prominent but nevertheless persisted after inflation; the nodules were more scarce, sometimes without ulceration and the large erosions on the folds were frequently absent. Nevertheless, at least two features of varioliform gastritis were seen: either enlarged folds and nodules, enlarged folds and erosions or nodules and erosions.

Correlation between endoscopy and histology (Table I)

Of the 35 cases diagnosed as diffuse varioliform gastritis, all had lymphocytic gastritis on histology. When the lesions were limited to the body,

TABLE I *Correlation endoscopy – histology*

	<i>Endoscopic diagnosis of varioliform gastritis</i>			
	<i>Diffuse</i>	<i>Corporeal</i>	<i>Antral</i>	<i>Total</i>
Cases (n)	35	20	11	66
Lymphocytic gastritis	35	18	1	54



Figure 1: Low magnification (60×): Surface and pit lining epithelium is infiltrated by numerous lymphocytes. The lamina propria inflammatory infiltrate is mild.

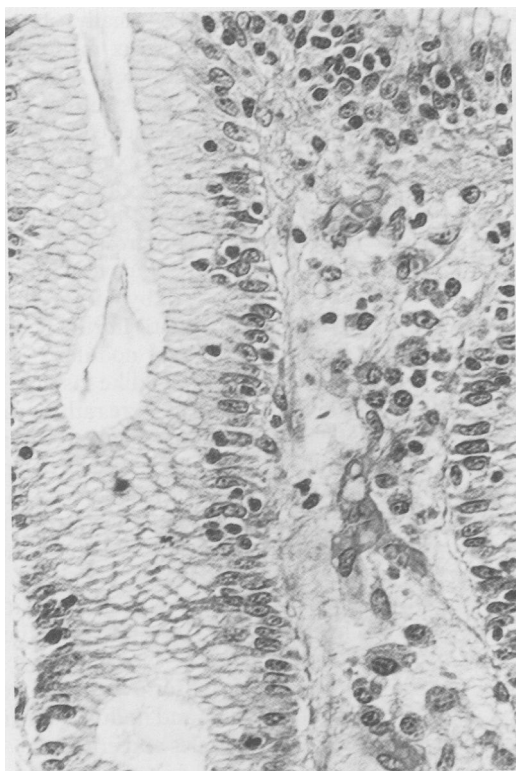


Figure 2: High magnification (480 $\times$): Dark nuclei of the intra-epithelial lymphocytes are surrounded by a clear rim or 'halo'.

the correlation between endoscopy and histology was less complete; nevertheless it remained very close because 18 of 20 cases corresponded to lymphocytic gastritis. The two exceptions were 'subacute' gastritis, characterised by oedema of the lamina propria, regenerative features of the epithelium, and a mixed inflammatory infiltrate.

Antral varioliform gastritis behaved quite differently; although the number of cases was small, the difference was striking as 10 of 11 cases were not lymphocytic gastritis. Seven cases corresponded to chronic active gastritis. In two cases, we again found oedema and acute inflammation analogous to those described in the two anomalous corporeal cases. Finally, one case showed oedema and fibrosis of the lamina propria without inflammatory cells.

HISTOLOGICAL DATA

Histological study of lymphocytic gastritis

In all cases, the intraepithelial lymphocytes were sufficiently numerous to give an easily identifiable picture even at low magnification. The epithelium appeared unusually basophilic, and was punctuated by numerous small cells with little cytoplasm (Fig 1). Very frequently, in the eroded areas, the picture was overshadowed

by abundant oedema and a mixed interstitial cellular infiltrate. The foveolae were enlarged, corrugated and penetrated by polymorphs. Sometimes, the dilated lumens contained mucus plugs and polymorphs ('crypt' abscesses). At high magnification, however, the characteristic lymphocytic component could easily be found (Fig 2). The erosive features and the lymphocytic infiltration were more evident in the body than in the antral region.

Lymphocyte counts made on the surface epithelium showed an average of 57 lymphocytes per 100 epithelial cells. The SD was 20.4 and the range (31–138). In comparison the results yielded by counts in chronic atrophic gastritis gave an average of 3.4 (SD: 2.3) with a range of 1–12.5. In histologically normal mucosa, the results were 2.5 (SD: 2.4) with a range of 1–9. Statistical comparison (Student's *t* test) between lymphocytic gastritis and chronic atrophic gastritis was highly significant ($p < 0.001$). Moreover, even in this large series, comparison of ranges showed no overlap between lymphocytic gastritis and chronic atrophic gastritis. As expected, the difference in counts between lymphocytic gastritis and normal mucosa was also highly significant ($p < 0.001$). Comparison between chronic atrophic gastritis and normal mucosa was not significant.

Correlation between histology and endoscopy (Table II)

During the period considered (1985–1987) among the 4840 gastric biopsies examined, we registered 67 cases of lymphocytic gastritis. Fifty four corresponded to varioliform gastritis while 13 cases had endoscopic features differing from varioliform gastritis. Among them, two could possibly be considered as having incomplete features of the disease. In one isolated corporeal enlarged folds was found while in the other were seen a bunch of nodules in a flat mucosa. The rest of our observations comprised two ulcers and one ulcer scar, three chronic atrophic gastritis with erosions on a flat mucosa and five patients without endoscopic lesions biopsied on suspicion of chronic B type gastritis.

Discussion

When describing lymphocytic gastritis in 1985,⁶ we were impressed by the similarity of particular clinical and endoscopic features.^{7,8} We have mentioned in recent reports^{10,11} that this picture was very similar to that described by Lambert *et al* 1978⁹ under the name of varioliform gastritis.

As these early works were based on retrospective data, we have been reluctant so far to assess the degree of correlation between the two conditions. The present prospective work allows us to positively state that the endoscopic features constituting as diffuse varioliform gastritis correspond to the histological diagnosis of lymphocytic gastritis. This is true as long as the definition of diffuse varioliform gastritis is precise. The disease, although predominating in the body, must involve the whole stomach; it must exhibit thick folds persisting after distension with air. The folds bear at their top aphthoid

TABLE II Correlation histology – endoscopy

Endoscopic features corresponding to the 67 cases of lymphocytic gastritis				
Varioliform features		Non-varioliform features		
Typical	'Incomplete'	Erosions	Ulcers	Non specific
54	2	3	3	5

nodules, spreading along in a stringlike fashion and are often crossed by irregular serpiginous erosions. Erosions on flat mucosa are more scarce.

Moreover, it appears in our experience that there also exists a less florid form of varioliform gastritis limited to the body which corresponds with a diagnosis of lymphocytic gastritis in nearly all cases, the rare exceptions being 'subacute' gastritis of imprecise aetiology.

On the contrary, the lesions limited to the gastric antrum can present very different histological appearances. Except for one case of 11, they do not correspond to lymphocytic gastritis. They can be either chronic active (erosive) gastritis of the B type or acute lesions having as their histological counterpart oedema and superficial erosions. The divergent histological findings in antral varioliform gastritis have already been mentioned in the work of Lambert *et al* 1978⁵ who distinguished it clearly from diffuse varioliform gastritis. This point was recently stressed again by Wyatt and Dixon¹² who refer to reports of Franzin *et al*¹³ and Nesland *et al*¹⁴ on antral erosions suggesting that the endoscopic diagnosis of antral varioliform gastritis did not correspond to a single histological entity but included examples of chronic (campylobacter positive) gastritis, bile reflux gastritis and lymphocytic gastritis. This heterogeneity of antral varioliform gastritis clearly shows in the present work and is in complete contrast with diffuse and corporeal varioliform gastritis which constitute the macroscopical expression of a homogenous histological entity: lymphocytic gastritis.

While there appears to exist perfect concordance between the endoscopic diagnosis of diffuse or corporeal varioliform gastritis and the histological diagnosis of lymphocytic gastritis the converse does not always apply as in our experience nearly 20% of lymphocytic gastritis do not correspond to varioliform gastritis. It could be argued that some of these cases are in fact incomplete varioliform gastritis that could perhaps be diagnosed as such with better training of the examiners. In the present series, we only found two such cases, one showing nodules and the other large folds without other lesions.

Whether these cases are taken into account or not, it is nevertheless clear that a part of our lymphocytic gastritis cases cannot be correlated with any precise macroscopic entity. The most logical hypothesis is to assume that varioliform

gastritis is only a crude endoscopic expression of a disease the characteristic feature of which is lymphocytic intra-epithelial infiltration. In this hypothesis, the macroscopic disturbances could only appear at some periods in the evolution of the disease. In favour of this concept are the isolated results we have obtained in patients followed by repeat biopsies. These showed that in some cases, the macroscopic lesions can disappear while the histological stigmata of lymphocytic gastritis are still evident¹⁵ (unpublished data). Research currently in progress in which a large group of lymphocytic gastritis patients are under follow-up will give a more complete answer to this point.

Very little is known about the aetiology of lymphocytic gastritis. The dense intra-epithelial lymphocytic infiltrate is reminiscent of coeliac disease.^{9,10} This suggests the possible involvement of alimentary antigens. New research based on clinical, epidemiological, and immunological data are required to assess this point.

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