Local immunoglobulin production is different in gastritis associated with dermatitis herpetiformis and simple gastritis

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SUMMARY The degree of inflammation and atrophy in gastric body mucosal specimens (n=38) from 28 patients with dermatitis herpetiformis (DH) was graded histologically. Immunoglobulin (Ig) producing cells were enumerated by paired immunofluorescence staining in a 500 µm wide section area from the muscularis mucosae to the lumen (mucosal 'tissue unit'). The number of immunocytes of the three main classes (IgA, IgM, and IgG) was significantly raised with increasing degree of gastritis. All three classes were increased in specimens showing atrophy compared with those without atrophy. IgA cells predominated as in simple gastritis, but a striking difference was a marked increase of IgM cells in specimens with the most pronounced DH-associated gastritis. Relative class distribution of immunocytes within different mucosal zones showed that the percentage of IgA cells was significantly higher in the luminal than in the basal zone, whereas the contrary was true for IgG cells. IgM cells did not show any zonal preference. No relation was seen between small bowel and gastric lesions. The disproportionate increase of gastric IgM producing cells in DH might nevertheless reflect seeding of precursor cells of the secretory immune system generated in the proximal small intestine where the local IgM response is relatively pronounced.

Occurrence of gluten sensitive enteropathy in patients with dermatitis herpetiformis (DH) is well documented.¹ The additional presence of a gastric lesion was first indicated when circulating antibodies to parietal cells were found in such patients.² A high prevalence of gastric acid hyposecretion and atrophic gastritis associated with DH was later confirmed in several studies.³⁻⁹

The DH related atrophic gastritis has much in common with that found in pernicious anaemia, both in terms of severity, localisation to the gastric body, and a possible autoimmune pathogenesis. Auto-

immune gastritis of pernicious anaemia and other disorders cannot be distinguished from severe atrophic gastritis in patients with dyspeptic diseases by conventional histological examination.¹⁰ In a previous study of normal and diseased gastric mucosa we showed that immunoglobulin A (IgA) producing cells always predominated, indicating a highly activated secretory immune system.¹¹ A severe degree of simple chronic gastritis and glandular atrophy, however, was associated with disproportionately increased local production of IgG.¹¹ Although IgG is probably of significance in the gastric mucosa in terms of internal or 'second line' defence it may, at the same time, contribute to the pathogenesis of gastritis through immunopathological mechanisms.

The aim of the present study was to characterise such immunological features in the gastric mucosa of

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Results

Both inflammatory changes and atrophy in the gastric body were significantly more pronounced in DH than in CD (Fig. 1). In CD these gastric body histopathological changes were similar to those seen in patients with gastric and duodenal ulcer or various other disorders.¹¹

Ig producing cells of the three main classes were clearly visualised with green and red fluorescence by paired DIF staining. Cells with cytoplasmic IgD and IgE were occasionally seen but were discounted because of their small number (<1%).

Ig PRODUCING CELLS RELATED TO GRADE OF GASTRITIS

Both totally and within each mucosal zone of the DH specimens the number of Ig producing cells increased significantly from gastritis grade 0 to grade 2 and also from grade 1 to grade 3 (Fig. 2). Compared with the other immunocyte classes, however, the increase of IgM cells in grades 2 and 3 was strikingly disproportionate (Table).

Table Numeric increase factors for IgA, IgM and IgG producing cells in gastric body specimens graded histopathologically according to degree of inflammation in patients with dermatitis herpetiformis (DH) or simple gastritis (SG)*

Grade of gastritis	IgA		IgM		IgG	
	DH	SG	DH	SG	DH	SG
Grade 1	1.7	2.2	1.9	2.8	1.1	4.3
Grade 2	6.3	5.5	12.0	6.5	9.5	18.5
Grade 3	10.9		18.6		9.7	

*Numeric increase factors represent relative increase of Ig producing cells per mucosal 'tissue unit' compared with specimens without inflammation (grade 0) in subjects with or without DH, respectively.

No differences in immunocyte numbers were found when specimens of gastritis grade 0 and 1 in the DH material were compared with the corresponding grades in all patients with simple gastritis (Fig. 2) or in those with concurrent CD. Conversely, in gastritis grade 2 the number of IgM cells was significantly

Fig. 2 Median total number and 95% confidence interval (range for n=4 and n=7) of IgA, IgM, and IgG producing cells per mucosal 'tissue unit' in gastric body specimens from patients with DH associated (a) and simple gastritis (b) in relation to grade of gastritis. Upper and lower parts of columns indicate median cell numbers in luminal and basal zones, respectively (see text). Percentage class distribution of immunocytes is given below the columns. n=number of specimens. Significant differences between DH associated and simple gastritis in total number of cells is indicated (*).

Fig. 3 Median number (and 95% confidence interval) of IgA, IgM, and IgG producing cells per mucosal 'tissue unit' in gastric body specimens from patients with DH in relation to grade of atrophy. Percentage class distribution of immunocytes is given below the columns. Significant numeric increase compared with grade 0 is indicated (*).

increased in DH compared with simple gastritis – that is, 31 v 14.3 cells per mucosal 'tissue unit' (Fig. 2). No such comparison could be done for grade 3 because the simple gastritis material did not contain specimens with that grade.

Relative class distribution of immunocytes within different mucosal zones showed in all gastritis groups that the percentage of IgA cells was significantly higher in the luminal than in the basal zone, whereas the contrary was true for IgG cells. IgM cells did not show any zonal preference.

DISTRIBUTION OF Ig PRODUCING CELLS

RELATED TO GRADE OF GLANDULAR ATROPHY

A significantly increased number of all three immunocyte classes was found when specimens without atrophy were compared with those showing atrophy of grade 1 (Fig. 3). No further increase was observed for grade 2, apparently because the height of the mucosal 'tissue unit' was reduced. The percentage class distribution was similar in groups with different grades of atrophy (Fig. 3).

Fig. 4 Relation between distribution of gastric inflammatory index (○) and atrophy (▲) in 22 patients with DH with three grades of small intestinal changes (see text). Medians are indicated by horizontal lines.

GASTRIC LESION RELATED TO SMALL INTESTINAL MORPHOLOGY

In 22 patients gastric and small intestinal morphology could be compared. The inflammatory and atrophic indices for each patient were based on single or multiple tissue sections from 1 to 4 specimens. No relationship was found between gastric and small intestinal lesions (Fig. 4).

AUTOANTIBODIES IN SERUM

Gastric parietal cell (GPC) antibodies were detected in three of the 21 patients tested; two had in addition ANA, AC, and THM antibodies. SMA antibodies were detected in two patients and THG and THM antibodies in one patient. Four other patients showed weakly positive reactions against THM. In 10 patients with CD (n=4) or non-ulcer dyspepsia (n=6) no autoantibodies were detected.

Discussion

IgA was the predominating class of mucosal immunocytes regardless of the severity of the gastric lesion associated with DH. This feature was consistent with our previously reported results in patients with unspecified 'simple' gastritis.¹¹ The most remarkable finding in DH gastritis was a substantial number of IgM producing cells in specimens with the two highest inflammatory grades (16% and 20% of the immunocytes, respectively). Expressed by numeric increase factors compared with normal mucosa, IgM cells showed the most pronounced rise

in all inflammatory groups. This was different from simple gastritis and has to our knowledge not been reported previously.

Locally produced IgA and IgM contribute to secretory immunity¹⁹ but the antigenic stimulus underlying the pronounced gastric IgM response in DH is unknown. It is interesting in this respect that there is an increased number of IgM producing cells in the duodenal mucosa of DH patients who are not on a gluten free diet compared with those who are.^{20,21} None of our patients was on a gluten free diet when biopsy was carried out.

The subclass distribution of IgA producing cells has indicated a closer relationship between the secretory immune system of the gastric and duodenal mucosa than between the proximal and distal intestine.²² No histopathological relationship was found, however, between the gastric and the small intestinal lesions in this study, which is in keeping with other reports.^{3,5,6,9} Moreover, a recent study showed that the gastric lesion did not improve during gluten free diet.²³ This indicates that disturbed small bowel function is not the cause of the gastric abnormality. Several other possibilities have been discussed, such as iron, zinc or other trace metal deficiencies, genetic factors or Dapsone treatment.⁹

IgM antibodies can activate complement and may thereby contribute to the chronicity of gastritis and glandular atrophy. A higher degree of systemic complement activation has been observed in patients with DH who are not on gluten free diet compared with those who are.²⁴ With intensified gastritis an increase of IgG cells in gastric body mucosa of patients with DH indicated altered mucosal immunologic homeostasis.²⁵ It is of interest in this context that local IgG cells with antibody specificity for intrinsic factor have been observed in pernicious anaemia.²⁶ Dermatitis herpetiformis patients with gastric lesions have a higher prevalence of parietal cell (GPC) antibodies than those without gastric atrophy,⁸ suggesting that an autoimmune mechanism may be involved in the pathogenesis. The occurrence of GPC and thyroid autoantibodies in the present DH material corresponded roughly to other reports.²⁷

Our finding of a higher degree of inflammation and atrophy in the body mucosa of patients with DH than in those with CD is in keeping with previous studies.^{5,9} This difference is also true after adjustment for age.⁹ Patients with CD may have increased prevalence of gastric acid hyposecretion and gastric atrophy,²⁸ however, although other studies have indicated a relative low prevalence of achlorhydria.^{29,30}

The gastric lesion in DH, along with the skin lesion (for review, see ref 27), is the most important difference between DH and CD. It is not known whether there is any relationship between the gastric

lesion and the skin lesion. Moreover, the role of circulating immune complexes in the pathogenesis of DH is not clear.³¹⁻³³ It is interesting that the skin deposits contain dimeric IgA of the IgA1 subclass,³⁴ compatible with an origin from gastric and duodenal plasma cells.²²

This study confirms previous reports that severe atrophic body gastritis is frequently associated with DH without being related to the severity of the small bowel lesion. The overall pattern of local Ig production in DH associated gastritis corresponded to that seen in simple gastritis with the exception of a remarkably disproportionate increase of gastric IgM producing cells in DH. This might reflect seeding of precursor cells of the secretory immune system generated in the proximal small intestine where the local IgM response is relatively pronounced. As there is no evidence for gluten involvement, autoantigens may, instead, partly explain the persistent immunopathology of DH associated gastritis.

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