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CASE REPORTS

Hypertrophic gastropathy with gastric adenocarcinoma: Menetrier's disease and lymphocytic gastritis?

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Abstract

Lymphocytic gastritis is a form of gastric inflammation characterised by a pronounced increase in lymphocytes in gastric surface and foveolar epithelium. Lymphocytic gastritis is often associated with endoscopic evidence of 'varioliform gastritis'. Lymphocytic gastritis has recently been reported to be associated with other forms of hypertrophic gastropathies. We present a case of hypertrophic gastropathy with gastric adenocarcinoma, with both Menetrier's disease and lymphocyte gastritis. Immunohistochemical studies showed that the intraepithelial lymphocytes were predominantly α/β T cells as in the normal stomach and not γ/δ T cells as in coeliac sprue. This case together with the six recently published cases suggests that Menetrier's disease and lymphocytic gastritis may be part of the same disease spectrum.

Lymphocytic gastritis, first described by Haot *et al*,[1] is a form of gastric inflammation in which there is a pronounced increase in lymphocytes in the gastric surface and foveolar epithelium. Lymphocytic gastritis is often associated with endoscopic evidence of varioliform gastritis. Not all cases of varioliform gastritis are 'lymphocytic' and not all of those that show lymphocytic gastritis are 'varioliform.'[2] Menetrier's disease as varioliform gastritis is a hypertrophic gastropathy which is usually associated with protein losing gastropathy. Recently, Crampton *et al*[3] described two cases of chronic lymphocytic gastritis associated with protein losing gastropathy, and Haot *et al*[4] six cases of Menetrier's disease associated with lymphocytic gastritis. We report a case of hypertrophic gastropathy with gastric adenocarcinoma which had features of both Menetrier's disease and lymphocytic gastritis.

Case report

The patient, a 63 year old man, was admitted to Hôpital Beaujon in October 1989 for epigastric pain and vomiting. He had recently lost 5 kg in weight. Clinical examination was normal. There was no evidence of hepatomegaly, splenomegaly, lymph node hypertrophy, or subcutaneous oedema. Laboratory investigation showed a haemoglobin concentration of 145 g/l, mean cell volume 100 fl, leucocyte count $8{\cdot}9\times10^9$/l, lymphocyte count $2{\cdot}16\times10^9$/l, and platelet count 520×10^9/l. The erythrocyte sedimentation rate was 100 mm in the 1st hour. Liver function tests were normal. Thee was hypoproteinaemia with a total protein concentration of 53 g/l and an albumin concentration of 33 g/l. The gammaglobulin concentration was low (5 g/l); serum calcium and magnesium concentrations were normal corrected for serum albumin. The urine contained no protein and renal function was normal. Upper gastrointestinal endoscopy showed coarse gastric folds with erosions throughout the body which was unchanged after insufflation. There was a fungated ulcerated mass involving the prepyloric zone. Biopsy specimens of this lesion showed gastric adenocarcinoma. Endosonography showed that the gastric wall was 7 mm thick throughout the body of the stomach. Faecal α_1 antitrypsin clearance was normal.

Total gastrectomy with splenectomy was performed in November 1989. The stomach weighed 0·550 kg. Gross examination showed striking rugose thickening of the gastric mucosa which predominated in the body. A deep prepyloric ulceration with an irregular outline and extensive underlying induration was present. Specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with haematoxylin-eosin. The remaining fresh tissue was snap frozen in liquid nitrogen, stored at −80°C, and sectioned. Immunostaining was performed using a three step immunoperoxidase technique. The monoclonal antibodies used are listed in the Table.

Results

Histological examination showed that the prepyloric mass was a moderately well differentiated adenocarcinoma with a mucinous component. There were no lymph node metastases. The mucosa of the body and fundus showed extreme elongation and tortuosity of the surface crypts. The gastric glands were cystically dilated. Some were lined by a large number of mucous cells and glandular cysts extended into the submucosae (Fig 1). Smooth muscle fibres were present between the surface crypts. All of these histological findings are considered diagnostic of Menetrier's disease. There was a moderate in-

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Monoclonal antibodies used in the immunoperoxidase study of frozen sections

	CD	Specificity	Origin
Anti-Leu 1	CD 5	T cells	Becton Dickinson*
Anti-Leu 2a	CD 8	T cytotoxic/suppressor cells	Becton Dickinson*
Anti-Leu 3a	CD 4	T helper/inducer cells	Becton Dickinson*
Anti-Leu 4	CD 3	T cells	Becton Dickinson*
Anti-Leu 5	CD 2	E rosettes receptor, T cells	Becton Dickinson*
Anti-Leu 9	CD 7	T cells and natural killer cells	Becton Dickinson*
β F 1		β subunit of T cell receptor	T cell science†
δ TCR		δ chain of T cell receptor	T cell science†
Pan B	CD 22	B cells	DakoPatts‡
Anti-interleukin-2 receptor	CD 25	Activated T cells	Becton Dickinson*
Anti-HLA DR		B cells, activated T cells, some epithelial cells, antigen presenting cells	Becton Dickinson*

*Becton Dickinson, Mountain View, CA, USA.
†T cell science, Cambridge, MA, USA.
‡DakoPatts, Santa Barbara, CA, USA.

crease in chronic inflammatory cells in the lamina propria and an appreciable increase in intraepithelial lymphocytes in the surface and foveolar epithelium. Lymphocytes were readily identified by their deeply basophilic chromatin, convoluted nuclear contours, scant cytoplasm, and surrounding clear halo (Fig 2). The intraepithelial lymphocyte count in the body was 31 per 100 epithelial cells. In the antrum there were 20 intraepithelial lymphocytes per 100 epithelial cells. The intraepithelial lymphocytes expressed T cell antigens and the HML 1 antigen; most were suppressor/cytotoxic T cells (CD 8+). Intraepithelial lymphocytes with the α/β form of the T cell receptor were more numerous than those with the γ/δ form of the T cell receptor. The foveolar surface and foveolar epithelium showed intense immunoreactivity for the HLA DR antigen. There was no evidence of *Helicobacter pylori*.

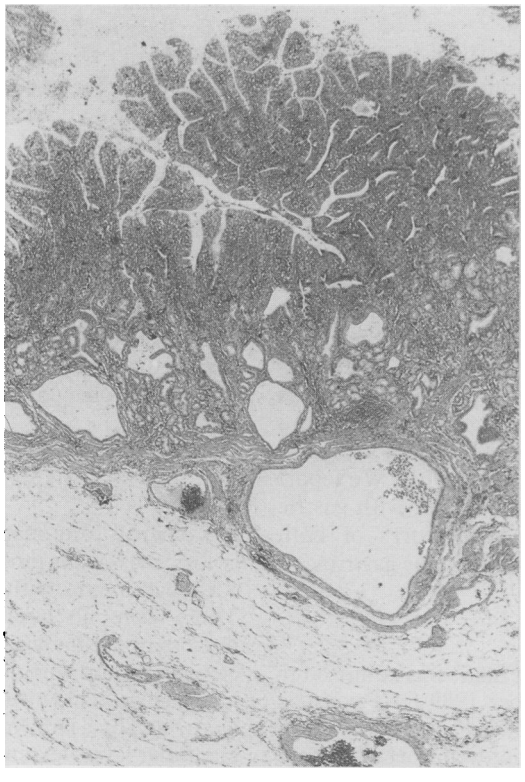

Figure 1: Histological feature of Menetrier's disease with pronounced thickening of the body mucosa associated with a glandular cyst extending into the submucosa. (Haematoxylin and eosin, original magnification ×25.)

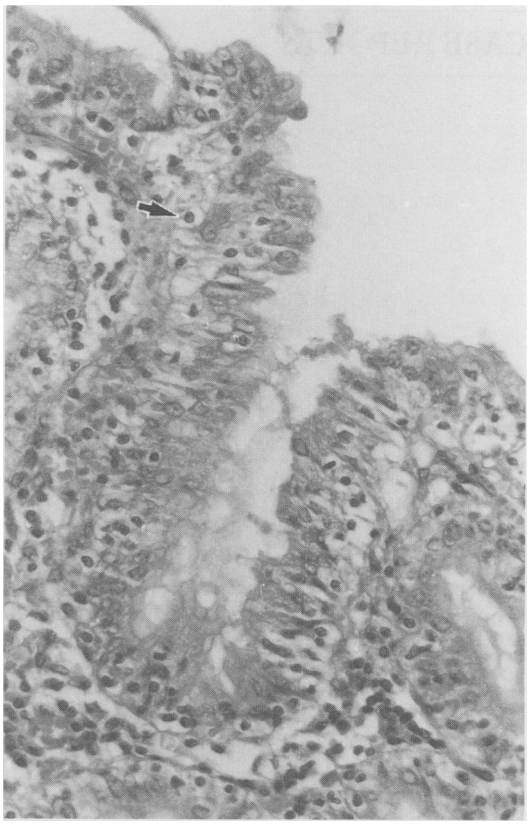

Figure 2: Lymphocytic gastritis characterised by many intraepithelial lymphocytes surrounded by a clear halo (arrow). (Haematoxylin and eosin, original magnification × 250.)

Discussion

Lymphocytic gastritis is a newly recognised and incompletely described entity characterised by lymphocytic infiltration of the superficial and pit epithelium of the gastric mucosa. The mean epithelial lymphocyte count per 100 epithelial cells obtained by Haot *et al*[1] and by Dixon *et al*[2] (28·2 and 55·3 respectively) are similar to the counts obtained in our case. These levels are considered to be diagnostic of lymphocyte gastritis.

Lymphocytic gastritis was first reported in association with varioliform gastritis.[1] On endoscopic examination the gastric mucosa has thickened folds, nodules, and aphthous erosions. In a prospective study Haot *et al*[5] showed that there is a close relation between lymphocytic gastritis and varioliform gastritis, although lymphocytic gastritis is not synonymous with varioliform gastritis.

Our patient did not show clear evidence of varioliform gastritis on endoscopic examination. Nevertheless, the gastric mucosa was hypertrophic, a feature present not only in lymphocytic gastritis but also in other forms of gastric disease, such as protein losing hypertrophic gastropathy, Menetrier's disease, Zollinger-Ellison syndrome, varioliform gastritis, and Cronkhite-Canada syndrome. Crampton *et al*[3] recently described two cases of lymphocytic gastritis associated with protein losing gastropathy severe enough to produce hypoproteinaemia and oedema of the lower extremities. In one of these cases there were prominent broad rugal folds but 'no histological evidence of Mene-

trier's disease' or sprue. There was a large number of intraepithelial lymphocytes in the duodenal mucosae. In the other case, a florid varioliform gastritis was seen macroscopically and *Helicobacter pylori* was present on the mucosa. Darchis *et al*[6] also reported a case of lymphocytic gastritis with varioliform gastritis and protein losing gastropathy. A recent review of six consecutive cases of Menetrier's disease reported associated lymphocytic gastritis in all six cases.[6] Menetrier's disease – also called giant hypertrophic gastritis, giant rugal hypertrophy, and exudative hypertrophic gastritis – is an extremely rare type of hypertrophic gastropathy. Several morphological characteristics define Menetrier's disease.[5 7] Hyperplasia of the gastric folds is frequently found in the corporeal region. There is a thickening of the mucosa due to foveolar hyperplasia and development of glandular cysts. Some glandular cysts extend to the submucosal layer. These cysts are lined with metaplastic mucosal epithelium. Smooth muscle fibres are present in the lamina propria between the superficial mucosal crypts and inflammatory cells. Our case showed all of these characteristics and was, in addition, associated with lymphocytic gastritis and a gastric adenocarcinoma.

In lymphocytic gastritis, the intraepithelial lymphocytes express the T cell antigens and HML 1 antigen.[8] Most of them are CD 8 cytotoxic/suppressor T cells.[8] Activated T lymphocytes are present in the epithelium as shown by the expression of interleukin-2 receptor (CD 25).[8] In the normal gastric epithelium 10% of the CD 3+ human intraepithelial lymphocytes are $\gamma/\delta+$, approximately the same proportion as in the blood.[9] Only in coeliac sprue is the proportion of γ/δ T cells above 30% of the intestinal intraepithelial lymphocytes. The T cell receptor of the gastric intraepithelial lymphocytes of the lymphocytic gastritis associated with coeliac sprue reported by Wolber *et al*[10] was not studied. The immunohistochemical findings in our case were similar to those described by Jones *et al*.[8] The ratio of γ/δ T cells was the same as that seen in the normal gastric epithelium and different from that of coeliac disease. The histological similarity of lymphocytic gastritis to the villous epithelial lymphocytic infiltration of the small intestinal mucosa observed in coeliac sprue is striking. Wolber *et al*[10] noted histological features of lymphocytic gastritis in 45% of patients with coeliac sprue or sprue like disease. Conversely, Jones *et al*[8] showed that in lymphocytic gastritis, biopsy specimens of the second part of the duodenum were normal. Nevertheless, the similarity between coeliac sprue and lymphocytic gastritis is real, and it has been suggested that the intraepithelial lymphocytes might be an abnormal response to a local antigen such as *Helicobacter pylori* or its products.[2]

We conclude that the immunohistochemical features of lymphocytic gastritis associated with Menetrier's disease are similar to those found in lymphocytic gastritis associated with varioliform gastritis, another form of hypertrophic gastropathy. We also found in our case that the increased numbers of intraepithelial lymphocytes that characterise Menetrier's disease were predominantly α/β T cells and not γ/δ T cells as in coeliac sprue. This report further supports the concept that Menetrier's disease and lymphocytic gastritis belong to the same disease spectrum. To improve the understanding of the lymphocytic gastritis and its associated pathological conditions, further work based on prospective and retrospective data is mandatory.

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