Case report

Gastric form of alpha chain disease

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SUMMARY A case of alpha chain disease, involving the stomach only, is reported in an Algerian man suffering from epigastric pains. Upper digestive tract fibroptic endoscopy showed two antral ulcers and an ulcerative gastritis pattern, which promptly disappeared with cimetidine treatment. Antral biopsies at a distance from the ulcers, but not of the ulcer crater itself, disclosed a dense infiltration of antral lamina propria by mature or sometimes atypical plasma cells. On transmural surgical antral biopsy, the infiltrate spread to the superficial part of the submucosa. No other localisation of the disease was found in spite of multiple biopsies obtained by endoscopy, with a peroral capsule and during staging laparotomy. The alpha chain disease protein was absent from serum and urine, but found in the gastric juice and in the cytoplasm of the cellular infiltrate ($\alpha 1$ subclass). A complete clinical, endoscopic, histological and immunological remission was observed after a six months' course of oral tetracycline.

Nearly all reported cases of alpha chain disease were mainly localised to the small intestine and usually mesenteric lymph nodes.¹⁻³ Very few cases apparently sparing the small bowel have been described,⁴⁻⁹ but in none of them the definite evidence of small intestinal integrity was obtained. We report here a well documented case of exclusive gastric involvement in alpha chain disease. The presence of the abnormal IgA1 in the gastric juice, but not in the serum, and the complete remission obtained with antibiotic treatment alone are other points of interest.

Case report

An Algerian man aged 32 years was admitted to hospital in March 1983. From 1981 he had been suffering from intermittent postprandial and nocturnal epigastric pains, relieved by foods. In November 1982, an upper digestive tract fibroptic endoscopy revealed a diffuse erythematous pattern

of antral mucosa, with multiple antral erosions. The pain was relieved by antacid treatment, but recurred in January 1983, with a weight loss of 5 kg. Personal and familial past histories were unremarkable. The patient was of middle class origins and physical examination was normal. Haemogram, marrow smear, serum iron, folate, vitamin B₁₂ and calcium, Quick's time, AST, ALT and serum alkaline phosphatase were all normal, as were stool weight, faecal fats, D-xylose test and $\alpha 1$ -antitrypsin clearance. No parasites or ova were found in stools, but *Giardia lamblia* were observed on duodenal biopsies. Fibroptic endoscopy revealed multiple antral erosions, a round ulcer crater, 6 mm in diameter, of the proximal antrum, and a 1 cm long linear prepyloric ulceration. The patient was given cimetidine, 1 g daily for one month, with prompt and complete relief of pain. After 10 days of treatment, endoscopy showed the complete disappearance of gross gastric mucosa abnormalities. The diagnosis of alpha chain disease, suspected by histological studies, was confirmed by immunohistochemistry and by gastric juice immunochemistry. Staging laparotomy showed a thickening of antral walls, numerous slightly enlarged lymph nodes in the mesentery and meso-

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colon whereas paragastric lymph nodes were normal. Treatment by tetracycline, 2 g daily, was given for six months from May 1983, together with metronidazole, 1.5 g daily, for the first 10 days. In October 1983, the patient was asymptomatic and had gained 6 kg. Endoscopy showed two ulcer scars and antral hypomotility. Histological and immunological studies showed the complete remission of alpha chain disease. The patient is currently in good health.

Methods

PATHOLOGICAL STUDIES

Multiple gastric biopsies were obtained during endoscopies in March and October 1983. Multilevel biopsies of the duodenum, jejunum, and ileum (per oral capsule), rectum and colon were done in March and October 1983. In April 1983, a full thickness antral biopsy, five multilevel wedge biopsies of the jejunum and ileum, several mesenteric and mesocolon lymph nodes, right hepatic wedge biopsy, and iliac crest biopsy were obtained during laparotomy. Peripheral venous blood, 24 hour urine and fasting gastric juice were sampled in March and October 1983 for immunologic studies. The gastric juice was immediately mixed (V/V 9:1) with a buffered solution containing per ml 131 mg ϵ -aminocaproic acid, 10 mg sodium azide, 1 mg kanamycin, 20 mg iodoacetamide, and 10 mg soybean trypsin inhibitor, and maintained at -70° until assay.

For optical microscopy, tissues were fixed in Bouin's fluid and 3 μ m sections were stained by haematoxylin-phloxin-saffran, Giemsa, Mac Manus (PAS) and Alcian blue methods. For electron microscopy, tissues were fixed in glutaraldehyde, postfixed in osmium tetroxide, embedded in Epon and thin sections were stained by uranyl acetate and lead citrate.

Immunofluorescence studies of immunoglobulin heavy and light chains were done on gastric, small, and large intestinal and rectal biopsies and on three mesenteric lymph nodes, according to a previously published technique.¹⁰ Antisera (Dakopatts, Copenhagen, Denmark) against human α , γ , μ , κ and λ chains, labelled with fluorescein isothiocyanate (FITC) or with tetra-rhodamine isothiocyanate (TRITC) were used. For identification of alpha chain disease synthesising cells, slides were first incubated with TRITC anti α -serum, then washed in phosphate buffer, and incubated again in a mixture of FITC anti κ and anti λ antisera, with appropriate dilutions. Further studies were done on cryostat sections with monoclonal antisera against $\alpha 1$ and $\alpha 2$ chains by indirect immunofluorescence with FITC-labelled secondary antibody to mouse Ig (Becton-Dickinson, Mountain View, USA), and with FITC labelled antisera against Secretory

Component (SC) (Dakopatts, Copenhagen, Denmark) and J chain (Nordic Immunological Laboratories, Tilburg, Netherlands). Immunoglobulin studies were carried out on venous blood serum, urine, and gastric juice concentrated 100 and five-folds, respectively. Quantitations were done in the serum by the single radial immunodiffusion technique and, for IgE, by the PRIST method.¹¹ Conventional immunoelectrophoresis used monospecific antisera to γ , μ , κ and λ chains. A particular antiserum to α chains was selected for this technique. It contained two types of antibodies: one directed against conformational antigenic determinants to the Fab α region, and the other precipitating only the IgA molecules in which κ and λ chains were combined with α chains. Immunoselection combined with immunoelectrophoresis was performed with antisera to κ and λ chains mixed in the agar and antiserum to α chains put in the trough.¹²

Results

HISTOPATHOLOGICAL STUDIES

In March 1983, endoscopic biopsies of the antral

Fig. 1 Fibre gastroscopic biopsy. Massive cellular infiltrate of the lamina propria, with crypt and antral gland sparsity. (H&E, $\times 100$).

ulcer crater showed a mucosal ulceration reaching the submucosa, and a moderate non-specific infiltration of the neighbouring lamina propria by lymphocytes, plasma cells, and polymorphonuclears. All antral biopsies done at a distance from the two ulcerations showed a different mucosal pattern (Fig. 1). The superficial epithelium was normal, crypts were rarefied, and atrophic. The lamina propria was the site of a dense monomorphic cellular infiltration by mature and sometimes atypical plasma cells (Fig. 2). No PAS or Alcian blue inclusions were seen. Biopsy of the fundic mucosa was normal. Several large lymphoid follicles with a germinal centre were present in the deeper part of the mucosa on the surgical specimen. The plasma cell infiltrate invaded the muscularis mucosae and the upper part of the submucosa (Fig. 3), whereas muscularis propria and serosa were normal. Ultrastructural studies confirmed that most cells infiltrating the antral mucosa were typical mature plasma cells. Apart from the presence of *Giardia lamblia* in duodenal samples, all biopsies obtained by endoscopy, per oral capsule or surgery from small and large intestine, rectum and

Fig. 2 Fibre gastroscopic biopsy. Cytological pattern of the antral mucosa infiltrate: mature (small arrows) and dystrophic (large arrows) plasma cells. (H&E, $\times 1100$).

Fig. 3 Surgical gastric biopsy. Diffuse and dense cellular infiltrate extends to submucosa (S), through the muscularis mucosa (M). (H&E, $\times 260$).

liver, were normal. All lymph nodes studied and iliac crest biopsy were also normal.

IMMUNOFLUORESCENCE STUDIES

Studies of the antral mucosa showed that 90% of the cells making up the infiltrate contained α chains, with a slightly weaker fluorescence than normal IgA containing cells (Fig. 4A). Double labelling revealed that these α chain synthesising cells contained no cytoplasmic light chains. A few cells, negative for α chains, were brightly fluorescent with anti κ and anti λ antisera, and their number was approximately equal to that of cells containing γ and μ chains. Studies with antisera to $\alpha 1$ and $\alpha 2$ chains showed a few brightly fluorescent normal plasma cells. Most cells infiltrating the antral mucosa were weakly fluorescent with anti $\alpha 1$ (Fig. 4B) and anti J chain antisera, but not stained by the anti $\alpha 2$ antiserum. The SC was only found in the infundibula and mucous necks of antral glands. Follicular germinal centre cells were polyclonal, as showed by antisera to $\alpha 1$, $\alpha 2$, κ and λ chains.

The small and large intestine and the rectum contained a normal number of cells synthesising polyclonal IgA, as shown by the double labelling

Fig. 4 Immunofluorescence study of gastric biopsy. Numerous cells of the mucosal infiltrate are fluorescent. a: after paraffin embedding, with anti- α -antiserum conjugated to flourescein ($\times 400$). b: on cryostat sections, with anti- α -I-anti-serum, by indirect immunofluorescence ($\times 400$).

Fig. 5 Immunoselection-immunoelectrophoresis of gastric fluid. 0.5 ml of anti- κ and of anti- λ antisera are mixed with agar to provide 3 ml of a 2% agar mixture per microscope slide. a: serum from an usual alpha chain disease patient (5 μ l). b: gastric fluid (5 μ l of 10-fold concentrated). In the trough: 0.1 ml of anti- α antiserum is used. The α -CP precipitin lines are indicated by an arrow.

technique, and studies of a jejunal biopsy showed the presence of both $\alpha 1$ and $\alpha 2$ containing cells. The number of cells positive with anti μ and anti γ antisera was normal. Exceptional cells containing polyclonal IgA were found in the lymph nodes.

FLUID IMMUNOGLOBULIN STUDIES

Electrophoresis of venous serum showed a moderate decrease of serum albumin and no abnormal peak. Serum concentrations of IgG, IgA, IgM and IgE were normal. By immunoelectrophoresis and immunoselection studies, the alpha chain disease protein was absent from serum and urine, but found in the gastric juice (Fig. 5). Control studies of the fasting gastric juice of three normal subjects either found polyclonal IgA or did not detect significant amounts of IgA. Proteinuria was 0.03 g/24 h, and concentrated urine protein immunoelectrophoresis was normal.

COURSE

In October 1983, antral biopsies showed the

disappearance of the plasma cell infiltrate. The lamina propria was the site of slight fibrosis, and contained a subnormal number of plasma cells (Fig. 6). Antral glands were still rarefied and atrophic. Gastric fundus, duodenal, distal ileum, colonic, and rectal biopsies were normal. Immunofluorescence studies of fundic, antral, duodenal, ileal and caecal biopsies showed normal percentages of cells containing α , γ , μ , κ and λ chains. Double labelling of antral samples confirmed that α chains containing cells synthesised κ and λ chains. Serum total protein level and electrophoresis were normal. The alpha chain disease protein was no more detectable in the gastric juice and was still absent from serum and urine.

Discussion

Gastric involvement, sometimes tumoural,¹³⁻¹⁵ but usually asymptomatic, and found by systematic biopsies of endoscopically normal appearing mucosa¹⁵⁻¹⁷ is not rare in the usual intestinal form of

Fig. 6 Gastric biopsy. After six month antibiotic treatment, the pathological cellular infiltrate of the antral lamina propria has completely disappeared. (H&E, $\times 190$).

alpha chain disease, but the present case is the first one in which the disease was shown to be confined to the gastric antrum only. The stomach may be the single site of extramedullary plasmacytoma¹⁸⁻²² and of Waldenström's macroglobulinaemia,²³⁻²⁷ and a case of gastric alpha heavy chain disease has been reported.²⁸ In these immunoproliferative disorders, discrete tumours are usually found,²⁰⁻²⁹ but in a few patients, including the present one, clinical and endoscopic features of gastric peptic ulcer and/or erosive gastritis may be observed.²²⁻³¹ In our case, the diagnosis would have been missed in the absence of biopsies at a distance from the ulcer crater. Moreover, cimetidine induced a prompt clinical and endoscopic improvement. The persistence, at the same time, of the lamina propria infiltrate clearly indicates that clinical symptoms were due to the superimposed erosions and ulcerations.

Cases of alpha chain disease sparing the small intestine seem to be very rare. One case of selective gastric involvement⁵ and one colonic localisation with subsequent spread to the stomach⁴ have been reported. No immunological studies of small intestinal biopsies were done, however, in spite of an increased number of jejunal mucosa plasma cells in the second case. In the three patients with probable involvement of the respiratory tract alone and in the other one with thyroid plasmacytoma, small intestinal investigations were not carried out.⁶⁻⁹

The mechanisms of colonisation of gut lamina propria by IgA synthesising cells are incompletely unknown. It is currently accepted that the mucosae of digestive, respiratory, urinary, and genital tracts share a common immune system in which IgA synthesising cells, born in a given site, home in a diffuse manner, although predominantly at the site of antigenic challenge.³²⁻³⁷ Other experiments have shown, however, that a purely local colonisation may occur at the site of immunisation.^{33-35, 38} Unfortunately, the stomach was not studied in all these experimental works. The present case of isolated gastric localisation of alpha chain disease could be related to the second type of mucosal colonisation by IgA synthesising cells, whereas gastric mucosa involvement in the usual intestinal form of alpha chain disease could be the result of the first one. The complete remission obtained by antibiotic treatment alone strongly suggests that, as in the usual form of alpha chain disease,^{2-39, 40} bacteria played a major role in the stimulation of gastric plasma cell proliferation.

Alpha chain disease protein, which belonged to the $\alpha 1$ -subclass as in all other cases of alpha chain disease so far studied,³⁹ was absent from serum, but found in the gastric juice and in the antral cellular infiltrate. A similar situation was described in a case

of intestinal alpha chain disease, in which the abnormal protein was present and linked to the SC in the intestinal juice, but was absent from the serum and urine.¹⁵ In this case, the distribution of the alpha chain disease protein was tentatively explained by the localisation of the proliferating cells to the IgA secretory system. Our present case is more puzzling. Indeed, in normal man, both J chain and SC are necessary for the selective transport of IgA toward the gut lumen.⁴¹⁻⁴² In the stomach, the lamina propria plasma cells do synthesise the J chain, but the SC is only found in the infundibula and mucous neck of antral glands (43, unpublished data), and IgA present in gastric mucus is devoided of SC.⁴⁴ Results of immunohistochemical study of J chain and SC localisation in the antral mucosa of our patient fit in these findings in normal subjects. Unfortunately, whether the alpha chain disease protein found in the gastric juice was linked to the SC was not investigated.

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