Gastro-duodenal Crohn's disease

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SYNOPSIS Gastro-duodenal Crohn's disease is rare. Thirty-one previously reported cases are briefly reviewed; histological confirmation of the diagnosis was not always possible. Details are given of a patient with pyloro-duodenal involvement accompanied by terminal ileitis and appendicitis where surgical specimens were available for study. The differential diagnosis is considered from the clinical and pathological aspects.

The granulomatous inflammatory lesions of regional enteritis, or Crohn's disease, are not confined to the terminal ileum but may occur at other sites in the gastro-intestinal tract from the oesophagus to the anal canal. The large bowel is a less frequent site of the disease, the jejunum is rarely involved, lesions are very rare in the stomach and duodenum, and one case has been reported of an inflammatory lesion of the oesophagus (Heffernon and Kepkay, 1954). Tables I and II summarize the reported cases, in which adequate evidence is given of gastro-duodenal lesions; Table I gives details of patients with gastric involvement while Table II lists cases of duodenal disease without any proximal lesions. Some of these patients have been reviewed previously by Richman (1955) and Richman, Zeifer, Winkelstein, Kirschner, and Steinhardt (1955). Seven further examples have been found in the literature since then; these and the present case are included in Table I.

Tables I and II indicate that 29 of the 32 cases of

gastro-duodenal Crohn's disease also had evidence of similar lesions elsewhere in the gastro-intestinal tract. In these 29 cases there was involvement of the ileum and/or jejunum as well as some other sites by Crohn's disease. The incidence is higher in males than in females (24 males and six females; in two cases sex was not indicated). The average age at diagnosis is 30 years based on 30 cases where the age was given, with a range from 9 to 57 years, but 23 of the cases occurred in patients between 20 and 35 years of age.

In the 31 previous records histological confirmation of the diagnosis was only obtained in 11 instances and of these five were biopsies. Therefore in view of the rarity of the condition, the present patient from whom fresh surgically resected specimens were available for pathological study, was thought worthy of record.

CASE HISTORY

J.B. was a man aged 29, the manager of an off-licence who first attended the Radcliffe Infirmary in March 1963 complaining of epigastric discomfort for two years, worse for three months. He obtained no relief from food

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TABLE I
CASE REPORTS OF CROHN'S DISEASE INVOLVING THE STOMACH

No.	Author	Sex	Age (yr.)	Histological Evidence	Other Sites of Disease
1	Ross (1949)	F	21	Yes (specimen)	Ileum, colon
2	Comfort <i>et al.</i> (1950)	M	22	Yes (biopsy)	Duodenum, ileum
3	Comfort <i>et al.</i> (1950)	M	36	No	Duodenum, jejunum
4	Martin and Carr (1953)	F	23	Yes (biopsy)	Duodenum, ileum, colon
5	Martin and Carr (1953)	F	24	No	Ileum
6	Heffernon and Kepkay (1954)	M	48	No	Oesophagus, duodenum, jejunum
7	Brown and Sims (1954)	F	24	No	Duodenum, ileum
8	Richman (1955)	M	20	Yes (biopsy)	Duodenum, ileum
9	Richman (1955)	M	34	Yes (specimen)	Duodenum, ileum, colon
10	Richman (1955)	M	9	No	Ileum
11	Goldgraber <i>et al.</i> (1958)	M	18	No	Duodenum, ileum
12	Pryse-Davies (1963)	M	30	Yes (specimen)	Duodenum, ileum, caecum, appendix

TABLE II

CASE REPORTS OF CROHN'S DISEASE INVOLVING THE DUODENUM BUT NOT THE STOMACH

No.	Author	Sex	Age (yr.)	Histological Evidence	Other Sites of Disease
1	Ragnotti (1939)	M	50	Yes (biopsy)	Jejunum
2	Shapiro (1939)	?	?	?	Jejunum
3	Shapiro (1939)	?	?	?	Jejunum
4	Guadarrama (1942)	M	18	No	Jejunum, ileum
5	Guadarrama (1942)	M	24	No	Jejunum, ileum
6	Brown (1945)	M	29	No	Ileum
7	Janus (1948)	M	22	No	Jejunum
8	Case Records of the Massachusetts General Hospital (1949)	M	30	Yes (specimen)	Nil
9	Comfort <i>et al.</i> (1950)	M	26	No	Jejunum
10	Comfort <i>et al.</i> (1950)	M	57	No	Jejunum
11	Comfort <i>et al.</i> (1950)	F	31	No	Jejunum
12	Carlisle and Judd (1952)	M	27	Yes (necropsy)	Jejunum, ileum
13	Brown and Sims (1954)	F	34	Yes (biopsy)	Nil
14	Roberts <i>et al.</i> (1954)	M	39	No	Ileum, jejunum
15	Berk (1956)	M	30	No	Nil
16	Berk (1956)	M	32	No	Jejunum
17	Berk (1956)	M	22	No	Ileum
18	Detiege <i>et al.</i> (1956)	M	22	Yes (specimen)	Ileum
19	Segal and Serbin (1956)	M	24	No	Jejunum, ileum
20	Anderson <i>et al.</i> (1957)	M	27	No	Jejunum, ileum

or alkali medicines: the discomfort was unrelated to meals and sometimes awakened him at night. There had been neither vomiting nor melaena. He smoked 40 cigarettes a day and drank 'in moderation'. In the preceding two and a half years he estimated that he had lost over 2 st. in weight. There were no serious past illnesses. His mother had suffered from a gastric ulcer. Clinical examination showed a pale, thin young man of nervous disposition (height, 5 ft. 7 in., weight, 128 lb.). The only abnormal finding was epigastric tenderness. Urine tests for reducing substances and protein were negative; there was no occult blood in the faeces. Blood investigations showed haemoglobin as 12.6 g./100 ml. and the erythrocyte sedimentation rate as 38 mm./hour (Westergren).

A clinical diagnosis of peptic ulcer was made: a barium radiograph was performed and reported as follows:

FIG. 1. Barium radiograph taken in April 1961 showing narrowing of the pyloric region and ulcer crater.

'The stomach is large and contains some excess of fluid. The antral area and pylorus are deformed and rigid and there is probably an ulcer crater in the pylorus causing some degree of obstruction' (Fig. 1).

There was some improvement on conservative treatment until he was seen again in October 1961 complaining of an exacerbation of the epigastric pain, of foul-smelling eructations of wind, and of forceful vomiting. About two weeks before this deterioration he had suffered a transient episode of diarrhoea. Again little was discovered on clinical examination apart from slight epigastric tenderness. A blood sample showed: E.S.R., 43 mm./hour, haemoglobin, 13.8 g./100 ml. The report of a repeat barium meal read: 'The pylorus is replaced by a long tubular irregular stricture which is causing obstruction with a dilated stomach containing excess food and fluid. This shows a considerable deterioration since April. Neoplasm is not excluded.'

The patient was then admitted to the Radcliffe Infirmary; clinically there was the additional feature of a succussion splash.

Blood investigations were reported as follows: Urea, 20 mg./100 ml., chlorides, 103 mEq./l., sodium, 134 mEq./l., potassium, 5.3 mEq./l., total white blood cells, 5,200/c.mm. A chest radiograph was within normal limits. Examination of faeces revealed no abnormality on microscopy or culture.

At the end of November 1961 a laparotomy showed thickening of the pyloric region of the stomach with an enlargement of local lymph glands. On exploring the remainder of the gut the terminal ileum was discovered to be thickened and adherent to itself, to the caecum, and to the ascending colon. A partial gastrectomy (Billroth I) was performed together with a vagotomy; the distal ileum, caecum, appendix, and the ascending colon were also resected leaving an end-to-end anastomosis. Following the operation the patient made an uneventful recovery and remains well.

PATHOLOGY

Two specimens were received in the laboratory for examination. The first consisted of the distal portion of stomach measuring 11.5 cm. along the greater curvature and 8.5 cm. along the lesser curvature, including a cuff of duodenum 1.5 cm. to 2.0 cm. in length.

MACROSCOPIC APPEARANCES OF FIRST SPECIMEN The proximal gastric mucosa showed a normal rugose appearance while the distal 3.0 to 4.0 cm. of the specimen had a congested, thickened, somewhat nodular mucosal surface. There was a shallow undermined ulcer, 0.6 cm. diameter, in the pyloric canal. Six soft discrete lymph glands were dissected from the omental fat attached to the pylorus.

MICROSCOPY In the pylorus and adjoining first part of the duodenum there was a granulomatous inflammatory lesion; elsewhere the proximal stomach appeared normal. The small pyloric ulcer showed fissures at the edge causing the undermined appearance; the base was covered by granulation tissue and there was some underlying fibrosis with partial replacement of the muscularis externa indicating that the ulcer was of a subacute type. Small intestinal metaplasia was not a feature of the gastric lesion.

Figure 2 indicates in a low-power view the general picture of the pyloro-duodenal junction at the level of the ulcer. Within the lamina propria of the mucosa on both sides of the junction giant cell granulomata were present composed of loosely knit clusters of histiocytic cells and occasional multinucleate cells (Fig. 3). The mucosa was breached by fissures lined by granulation tissue infiltrated by lymphocytes, plasma cells, histiocytes, polymorphonuclear leucocytes, and a few giant cells. The submucosa was thickened by areas of fibrosis and oedema with marked infiltration by plasma cells and lymphocytes the latter forming follicles. A striking feature was the presence of abscesses or sinuses, some of which showed a connexion with mucosal fissures, having a central zone of purulent necrotic debris and an outer zone of granulation tissue infiltrated by the inflammatory cells listed above and also including giant cells. The infiltrate and granulomata spread focally through the muscle coats as far as the serosa which was markedly congested. Pyloric lymph glands contained enlarged germinal centres in the follicles, and occasional non-caseating giant cell granulomata containing loosely knit epithelioid cells were also found here. Sections stained with the Ziehl-Nielson and P.A.S. methods were negative for tubercle bacilli and fungi. No evidence of foreign substances or parasites was obtained in multiple sections.

FIG. 2. A low-power view of a section through the pyloro-duodenal junction showing pyloric and duodenal mucosa, the pyloric ulcer with undermined fissured edges, a fissure in the duodenum, and underlying abscess cleft. The wall is thickened by fibrosis and inflammatory exudate. Haematoxylin and eosin $\times 5$.

FIG. 3. A giant cell granulomatous lesion within the lamina propria of the pyloric mucosa. The muscularis mucosae may be seen at the bottom right. Haematoxylin and eosin $\times 110$.

The second specimen consisted of the distal 52 cm. of ileum, the caecum, appendix, and ascending colon.

MACROSCOPIC APPEARANCE OF SECOND SPECIMEN The terminal 13 cm. of the ileum was lined by a hyperaemic thickened mucosa of 'cobble-stone' type with ulceration and fissuring—a naked-eye appearance typical of regional ileitis. The ileo-caecal valve and caecal mucosa were also swollen and congested but not ulcerated. A bulbous appendix contained pus in the lumen. The ascending colon was of normal appearance. Seven soft lymph glands were dissected from the ileo-caecal mesentery.

MICROSCOPY The terminal ileum was covered by a hyperaemic oedematous serosa containing dilated lymphatics and lymphoid aggregates. All coats showed a focal but marked infiltration of plasma cells, lymphocytes, and some polymorphonuclear leucocytes. The mucosa was partly ulcerated and replaced by a layer of granulation tissue. Some of the

mucosa contained glands of clear cell type similar in appearance to Brunner's glands. Lymphoid aggregates in the submucosa contained prominent germinal centres but no unequivocal epithelioid cell or giant cell granulomata were identified. The ileal surface of the ileo-caecal valve, the caecum, and proximal ascending colon showed an excess of plasma cells and lymphocytes in a hyperaemic mucosa together with an increase in eosinophils. The appendix was the site of an acute purulent inflammation with pus cells filling the lumen and infiltrating through to the peritoneum, but there was also evidence of a chronic granulomatous inflammation with fissures in the mucosa, submucosal abscesses, and occasional giant cell granulomata. Enlarged follicles and germinal centres were seen in the mesenteric glands without any tuberculoid lesions. Ziehl-Nielsen and P.A.S. preparations were also negative in sections from this second specimen.

DISCUSSION

The chief interest in the present case of gastro-duodenal Crohn's disease lies in its rare occurrence and in the differential diagnosis. Clinically in the initial stages the problem was that of vague epigastric pain and tenderness consistent with peptic ulceration: within six months of the patient first being seen there was evidence of pyloric stenosis. Laparotomy enabled the correct diagnosis to be made on finding an inflammatory lesion of the stomach and duodenum with co-existing terminal ileitis. In previous cases a pre-operative diagnosis has depended on the presence of other evidence of regional enteritis elsewhere in the bowel. It is remarkable that the fairly extensive terminal ileitis in this patient should have caused no significant symptoms. Crohn's disease of the stomach and duodenum occurs in younger adults and the main differential diagnosis is peptic ulceration leading to pyloric stenosis. Other causes of obstruction may have to be considered such as carcinoma, argentaffin tumours, lymphomata.

The clinical manifestations of gastro-duodenal Crohn's disease have been fully discussed by Comfort, Weber, Baggenstoss, and Keily (1950), and summarized under four headings: 1 abdominal pain and nausea, 2 episodic diarrhoea, 3 gastric retention, and 4 effects of malabsorption. The manifestations are therefore diverse and protean simulating those of many other gastro-intestinal diseases.

DIFFERENTIAL DIAGNOSIS In a discussion of the pathological differential diagnosis of a biopsy or other specimen it must be admitted that several conditions might give a similar histological picture,

especially in a small biopsy showing only non-specific chronic inflammatory changes. The following conditions should be considered, particularly in lesions of the stomach:

Chronic gastritis Chronic gastritis, which may occur in the vicinity of an ulcer or carcinoma and may be accompanied by giant cell granulomata (Scott, Smith, Cox, and Palmer, 1953).

Tuberculosis Tuberculosis is unlikely in the absence of a generalized infection; a search for organisms and typical caseous lesions should be made.

Gastric syphilis Gastric syphilis may occur rarely in the secondary or tertiary stage (Cooley and Childers, 1960): it is usually a diffuse lesion of the stomach wall, and serological tests and a therapeutic response help to confirm the diagnosis.

Sarcoidosis Sarcoidosis is more difficult to differentiate; gastro-duodenal involvement is no less rare than in Crohn's disease and pyloric obstruction may also occur (Scott *et al.*, 1953). Levere (1962) has reviewed 24 cases of sarcoidosis with gastric lesions. The diagnosis would depend on evidence of sarcoid elsewhere in the body, Kveim's test, and the histological appearance of any granulomata. In sarcoidosis the tuberculoid lesions are rarely accompanied by central necrosis, the epithelioid cells are large and prominent, and Schaumann bodies may be found (McKusick, 1953).

Eosinophilic granuloma Eosinophilic granuloma may be distinguishable by the eosinophilic infiltrate but other chronic inflammatory cells are present in the exudate and eosinophils may be prominent in Crohn's disease. The gastric lesions of eosinophilic granuloma have been well reviewed by Blackwell and Gild (1962). The presence of an eosinophilia in the blood and an allergic diathesis in the clinical history are helpful distinguishing features. An eosinophilic granuloma has also been attributed to the herring parasite, *Eustoma rotundatum*, usually in the small intestine, but also reported in the stomach by Voorhuis and Eijlers (1961). Similar lesions may result from an allergic gastritis; Boivin and Berry (1961) have attributed such a lesion to reserpine therapy. An unusual form of granulomatous gastritis has been found in a patient with renal polyarteritis nodosa by Hiller (1962).

Fungal diseases Fungal diseases, *e.g.*, *Histoplasma capsulatum*, may cause non-specific inflammatory lesions in the stomach (Engle, 1953).

Foreign substances Beryllium and silicones (from toothpaste), for example, can also give rise to granulomata in the gastric mucosa (Goldgraber,

Kirsner, and Raskin, 1958). Sherman and Moran (1954) have demonstrated the occurrence of similar lesions in the stomach of non-specific type thought to be associated with gastric juice and food particles; their thesis is supported by the production of comparable lesions in experimental animals.

The above widely differing causes indicate the need for careful consideration of the diagnosis in non-specific gastroduodenal inflammatory lesions. In the case presented in this paper the criteria adopted for the diagnosis of Crohn's disease of the stomach and duodenum were a typical lesion involving all coats of the stomach and the presence of abscesses and sinuses connecting with fissures in the mucosa; the presence of loosely-woven tuberculoid lesions; the absence of tubercle bacilli, fungi, foreign material or parasites in the lesions; and the presence of a classical regional enteritis in the small bowel.

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