Short reports

Zollinger-Ellison syndrome in a child: medical treatment with cimetidine

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SUMMARY A 12-year-old boy presented with intestinal obstruction associated with duodenal and oesophageal ulceration. At laparotomy he was found to have an islet cell tumour in the right lobe of the liver. Gastroenterostomy was performed. Raised levels of serum gastrin were detected. Treatment with cimetidine has produced satisfactory control of his symptoms for 16 months, and is an acceptable alternative to total gastrectomy in childhood.

The syndrome described by Zollinger and Ellison in 1955¹ is rare in children. It is due to either single or multiple tumours composed of gastrin-secreting cells. Most tumours arise in the pancreas; a few are found adjacent to the pancreas.² This report describes the clinical and pathological details of a boy with

Zollinger-Ellison syndrome in which a gastrinoma was detected in the liver. Successful management has been achieved with cimetidine.

Case report

A 12-year-old boy weighing 35 kg presented in October 1977 with a 6-month history of intermittent epigastric pain, vomiting, and occasional haematemesis. He had been passing several bulky stools each day for 12 months and had lost 7 kg in weight. There was no family history of endocrine disorder or peptic ulceration; his parents and three older siblings were alive and well. Physical examination showed epigastric tenderness but no other abnormality. Barium meal examination showed widening of the duodenal loop and dilatation of the proximal

Fig. 1 Liver containing islet cell tumour. The tumour has a gyriform pattern. Haematoxylin and eosin $\times 360$.

duodenum, while endoscopy showed inflammation of the lower oesophagus and focal duodenal ulceration with extensive acute inflammation.

Duodenal obstruction necessitated laparotomy, at which was found an oedematous mass affecting the head of the pancreas and the second part of the duodenum. A white tumour, 4 cm diameter, in the right lobe of the liver was biopsied. Gastrojejunostomy was performed.

Histological examination of biopsies of stomach, duodenum, and jejunum showed mucosal oedema and acute inflammation of the superficial lamina propria throughout. Acute ulceration was present in the oesophagus, while the gastric antrum showed pronounced hyperplasia of the parietal cells. The liver biopsy contained a tumour, composed of ribbons of cells, which had the appearance of an islet cell tumour (Fig. 1). This was confirmed by EM examination which showed that most tumour

cells contained large numbers of cytoplasmic vesicles, 300–350 nm diameter, with greyish, finely granular contents (Fig. 2). A few cells had densely-cored vesicles, 55 nm diameter, similar to the granules found in the α -cells of the islets of Langerhans.

Postoperatively, up to 6 litres of gastric fluid a day were produced and further gastrointestinal haemorrhage necessitated a second laparotomy to under-run an anastomotic ulcer.

Investigations showed faecal fat 86 mmol/24 h (24.4 g/24 h) (normal <18 mmol/24 h; 5.1 g/24 h), fasting serum gastrin 798 ng/l (normal <105 ng/l), and plasma pancreatic polypeptide 240 pmol/l (normal <100 pmol/l). Levels of gastric acid were high despite the previous gastrojejunostomy. The following were normal: serum calcium 2.18 mmol/l (8.7 mg/100 ml), plasma glucagon 5 pmol/l, serum vasoactive intestinal polypeptide <5 pmol/l,

Fig. 2 Portions of liver tumour cells containing many cytoplasmic vesicles. There is some minor variation in the size and in the electrondensity of their contents. $\times 11\,200$.

and glucose tolerance. Coeliac and superior mesenteric angiograms showed no abnormality. Ultrasound examination showed a single lesion in the right lobe of the liver.

Intravenous cimetidine (6 mg/kg) quickly relieved his epigastric pain and he was therefore started on maintenance treatment with cimetidine, 1 g a day in divided doses. His condition continued to improve, with a return to a full diet and a weight gain of 23 kg over 12 months. He is now able to take part in all school activities. Fasting serum gastrin, 12 months after starting treatment, is still raised (420 ng/l and 284 ng/l on consecutive days), but he is well and symptom-free.

Discussion

Pancreatic tumours are rare in childhood but insulinomas,³ carcinomas of acinar and mixed origin,⁴ and gastrinomas can occur.⁵⁻⁶ The definitive diagnosis of gastrinoma usually requires demonstration of high levels of gastrin in fasting serum, but detection of granules in the cytoplasm of tumour cells by EM examination can also help. There may however be some variation in granule size and the granules in our patient, who had vesicles measuring 300–350 nm diameter, correspond to type II granules of Greider *et al.*² Immunofluorescence and immunoperoxidase techniques can be used to show the presence of hormone in the cytoplasm of tumour cells⁷ but, once again, methods have had varied success.² The association of gastrinomas with neoplasms in other endocrine organs is now well established,⁸ but, in a review of 15 children with the Zollinger-Ellison syndrome, none had a second endocrine tumour.⁵ However, even single tumours can produce more than one pancreatic hormone⁹ as, for example, in our patient who had raised levels of both gastrin and pancreatic polypeptide. Gastrinomas can occur in the pancreas, stomach, or duodenum⁷ but in some cases either a lymph node or a hepatic deposit was found without definite localisation of a primary pancreatic or periduodenal tumour.⁶ While it is possible that such a tumour might arise in the liver, embryological remnants of pancreatic and gastric tissue are rare in this site and are not mentioned by Willis.¹⁰

The prognosis for the Zollinger-Ellison syndrome depends more on the effects of gastrin than on the degree of differentiation of the tumour. Assessment of malignancy by the cytology of tumour cells is an unreliable predictor of behaviour² but 60% of the tumours that have produced the Zollinger-Ellison syndrome are malignant, with metastases particularly in the liver and lymph nodes.¹¹ Total gastrectomy has been found to improve prognosis, probably by the reduction of acid and secretin

production both of which contribute to steatorrhoea and cause ulceration of oesophagus, stomach, and duodenum.^{5,12} There have been some reports of the treatment of adults suffering from Zollinger-Ellison syndrome with H₂-receptor antagonists, such as metiamide and cimetidine,¹³⁻¹⁴ with a satisfactory response in up to two-thirds of them. The immediate relief of symptoms and the subsequent clinical improvement in our patient shows that cimetidine is similarly acceptable in childhood as an alternative to total gastrectomy in the management of the Zollinger-Ellison syndrome if the tumour cannot be surgically excised. No side effects of treatment have been observed.

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