The Zollinger-Ellison syndrome

A case report

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Summary

A vagotomy and antrectomy was performed on a 15-year-old boy with a malignant gastrinoma for emergency control of massive upper gastro-intestinal haemorrhage from a large posterior penetrating duodenal ulcer in the presence of jejunal ulceration and liver metastases. Hypergastrinaemia was confirmed by elevated serum gastrin levels. In the short term postoperatively the patient's disease has been controlled with oral cimetidine. Although controversy continues over the efficacy of cimetidine in the management of gastrinomas, medical treatment should be considered as an alternative to total gastrectomy in children with malignant gastrinomas because they are often slow-growing, indolent and compatible with long survival.

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In 1955 Zollinger and Ellison[1] described the association of pancreatic islet cell lesions, gastric hypersecretion and peptic ulceration. Marks *et al.*[2] from Groote Schuur Hospital, Cape Town, reported 23 years ago on one of the earliest confirmed cases in South Africa. The Zollinger-Ellison syndrome (ZES) affects only about one per million individuals but presents formidable problems in clinical management.[3]

The medical options and the changing role of surgery in the management of patients with gastrinoma are discussed.

Case report

A 15-year-old boy was admitted to Tygerberg Hospital with a short history of severe upper gastro-intestinal haemorrhage, diarrhoea and weight loss.

The boy was emaciated and anaemic with signs of hypovolaemic shock due to severe blood loss. After a period of resuscitation the patient was subjected to urgent operation after gastroscopic examination had confirmed the presence of a duodenal ulcer. At laparotomy, an actively bleeding 2 x 2 cm posterior penetrating duodenal ulcer was observed. Truncal vagotomy, antrectomy and Billroth II gastrectomy were performed.

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A second laparotomy performed 4 days later for intestinal obstruction confirmed the presence of four jejunal ulcers and a jejunojejunal intussusception. The intussusception was manually reduced without need for resection and the non-perforated jejunal ulcers were oversewn. Histological examination of hepatic metastases confirmed the clinical suspicion of malignant gastrinoma (Fig. 1). An obvious primary tumour in the pancreas or duodenal wall could not be identified at operation or later by ultrasonographic or computed tomographic (CT) investigation.

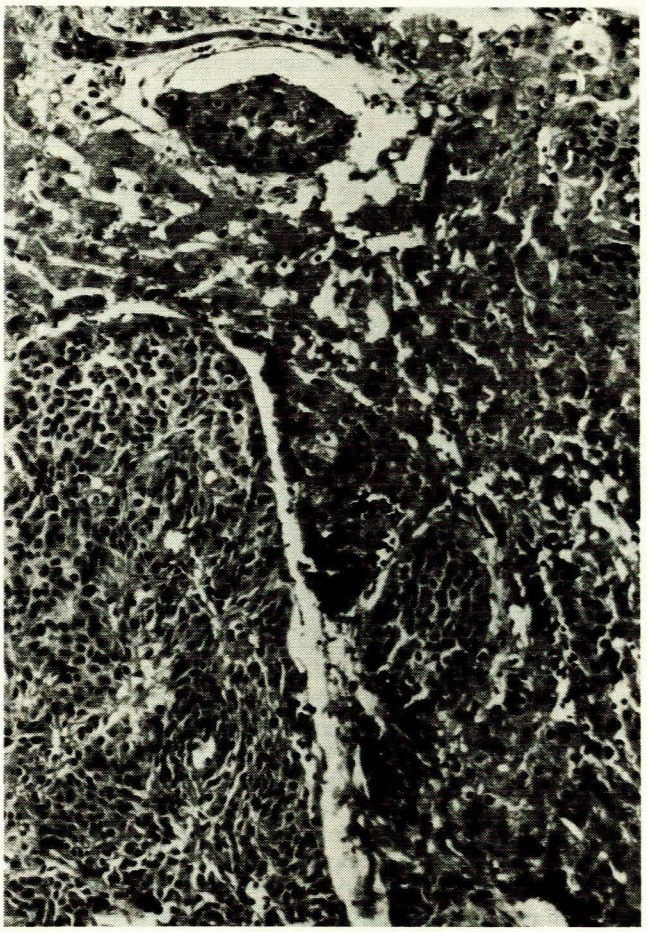

Fig. 1. Photomicrograph showing gastrinoma metastases in the liver (H and E 200).

Postoperatively the patient received total parenteral nutrition to improve his poor nutritional state, together with intravenous cimetidine 200 mg 6-hourly. In the short term there were no untoward side-effects of the treatment. Pre-operative estimation of serum gastrin confirmed that levels were significantly elevated. There were no biochemical or clinical signs of the multiple endocrine neoplasm type 1 (MEN-1) syndrome. Serum calcium values and radiography and CT of the pituitary fossa

were within normal limits. The patient made an uneventful recovery after a stormy postoperative phase and is at present being maintained on oral cimetidine 200 mg 6-hourly. The combination of duodenal ulceration, diarrhoea, hypergastrinaemia and histological evidence of hepatic metastases confirmed the presence of ZES.

Discussion

The ZES is characterized by gastric hypersecretion resulting in fulminant, intractable, ulcerogenic diathesis, hypergastrinaemia and an underlying non-ß-cell tumour of the pancreas.[4] Haemorrhage, perforation and obstruction are common complications. The majority of gastrinomas are situated in the pancreas and about 13% in the duodenum.[4] At the time of diagnosis 60% are malignant, two-thirds having metastasized at the initial exploration,[4] and about one-third of patients have other endocrine tumours — MEN-1 syndrome. Apart from hypergastrinaemia and excessive gastric acid secretion, tumour localization may be possible by angiography, ultrasound examination, CT and percutaneous transhepatic pancreatic venous sampling for gastrin. In patients with borderline or low serum gastrin levels the calcium and secretin provocative tests have proved helpful in diagnosing gastrinoma.[5,6]

In the pre-cimetidine era total gastrectomy was the treatment of choice in most patients regardless of age after clinical and laboratory confirmation of ZES. The operation was performed even in the presence of extensive regional, lymphatic or hepatic involvement and resulted in improved quality of palliation in most patients, notwithstanding advanced disease.[7-9]

The place of chemotherapy as an adjunct to surgery has been controversial but some patients with advanced ZES have responded to streptozotocin alone or in combination with 5-fluoro-uracil.[9] Total gastrectomy alone gives excellent results, nutrition rarely being a problem even in children.[7,8] Although about 50% of gastrinomas are malignant they tend to remain dormant after total gastrectomy, most patients leading a relatively normal life in the absence of weight loss and dumping.[8] Unfortunately, in only a small proportion of cases can the primary tumour be resected with permanent cure.[8,9] However, some authors have shown that total gastrectomy has been associated with an appreciable mortality and morbidity. They point out that almost all totally gastrectomized patients experience one or several side-effects including oesophageal reflux symptoms, early satiety and stenosis of the oesophagogastric junction. Often, these side-effects have been tolerable, but in some the quality of life has been adversely affected.[3]

The advent of H_2-receptor antagonists, and their recognized efficacy in controlling gastric acid hypersecretion, has reopened the debate on the treatment of ZES. Some workers[3,10-15] have suggested that long-term therapy with H_2-receptor antagonists is preferable to total gastrectomy, which is not free of complications, and that satisfactory control with cimetidine can be achieved in most patients. Guidelines for the medical management of ZES include administration of cimetidine 300 - 600 mg 4 times daily or ranitidine 300 - 450 mg 4 times daily with dose adjustment to ensure gastric acid secretion of < 10 mEq/h for the 2-hour period preceding the next dose of cimetidine.[3,10-15] Published results[14] have indicated that the presence or absence of symptoms does not reflect the adequacy of antisecretory control and stress the importance of periodic gastric analysis. Periodic endoscopy is also essential in evaluating the effectiveness of the medical regimen.[13]

Disadvantages of treatment include the prohibitive costs of long-term treatment; clinical failure in 25 - 50% of cases; development of resistance and cimetidine; side-effects such as gynaecomastia, impotence, and interference with hepatic detoxification; the pitfalls of compliance; and life-long commitment to a rigid schedule of pill-taking.[3,10-15] In addition, the risks and untoward effects of long-term administration of cimetidine in very high doses are unknown.

The new H_2-receptor blocking agent, ranitidine, or a combination of anticholinergic drugs and vagotomy may prove useful alternatives,[3,10-15] while the combination of highly selective vagotomy with pharmacological acid inhibition may also offer an acceptable alternative in long-term management.[12] The rationale for this treatment is that the addition of vagotomy may reduce the requirements of cimetidine, although this recommendation remains controversial. Malagelada *et al.*[10] do not recommend this treatment because their patients with ZES and previous vagotomy and gastric resection required doses of cimetidine for symptomatic control similar to those required by patients who did not undergo vagotomy.

In those patients who develop unacceptable side-effects because of drug therapy, or whose ulcer diathesis is not controlled by medical means, the treatment of choice remains total gastrectomy. In the case under discussion, surgery will only be implemented should cimetidine fail to control recurrent haemorrhage and shock.

Addendum

The occurrence of a large stomal ulcer 9 months after Billroth II gastrectomy and continuous cimetidine treatment necessitated a total gastrectomy. Regression of the liver metastases was evident. The patient made an excellent recovery.

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