Gastrinoma syndrome in multiple endocrine neoplasia

New approaches to localisation and management

Multiple endocrine neoplasia type I is associated in 60% to 70% of patients with tumours of the pancreatic islet cells,¹ which, like sporadic tumours of the islet cells, often secrete hormones. Unlike the sporadic tumours, however, multiple endocrine neoplasia type I may be associated with diffuse hyperplasia of islet cells or multiple pancreatic adenomas, or both.^{2,3} The adenomas may vary in size from a small nest of cells less than 100 µm in diameter to an adenoma greater than 2 cm.³ Thus the localisation and management of pancreatic endocrine tumours in patients with the multiple endocrine neoplasia type I syndrome is often difficult, as shown by the presented case.

Case history

A 46 year old man presented in 1985 with polyuria and proteinuria. Renal biopsy showed membranous glomerulonephritis, and his renal function was impaired (urea concentration 18-20 mmol/l and creatinine concentration 300-350 µmol/l). He was treated with 50 mg prednisolone daily for six months after which the dose was reduced to 15 mg on alternate days (which he subsequently continued). Between 1985 and 1988 he remained well and his renal function was stable, but in 1988 he developed an increased serum calcium concentration of 2.80-2.95 mmol/l (corrected to a serum albumin concentration of 40 g/l) and was referred here for investigation. At that time he had a six month history of indigestion and epigastric pain before and after food. His sister had died of a myocardial infarction and had been noted at necropsy to have hyperparathyroidism, and his mother had died aged 42 of a perforated duodenal ulcer.

Physical examination of the patient gave normal results, with no features of chronic hypercalcaemia. The table shows the results of investigations. Because he had never had documented hypocalcaemia and

the degree of renal impairment was mild the inappropriately raised parathyroid hormone concentration was thought to represent primary rather than tertiary hyperparathyroidism. Endoscopy showed multiple gastric and duodenal erosions, and his basal acid output was increased, at 18.3 mmol/h (normal <5 mmol/h). Though the hypergastrinaemia could have been explained by the renal impairment reducing the clearance of gastrin and increasing the basal acid output, the possibility of a gastrinoma could not be excluded. Abdominal computed tomography and highly selective visceral angiography showed a 2 cm lesion in the middle third of the pancreas, with no visible hepatic metastases.

Results of clinical investigations in patient with multiple endocrine neoplasia type I

	Test result (normal value)
Full blood count and liver function tests	Normal
Urea (mmol/l)	19 (<7)
Creatinine (µmol/l)	365 (<120)
Glomerular filtration rate (ml/min)	26-30 (120-150)
Corrected serum calcium (mmol/l)	2.99 (2.2-2.65)
Serum phosphate (mmol/l)	0.69 (0.8-1.4)
Serum parathyroid hormone (pmol/l)	467 (44-167)
Gut hormones:	
Vasointestinal peptide, somatostatin, and neurotensin	Normal
Pancreatic polypeptide (pmol/l)	394 (<300)
Gastrin (pmol/l)	162 (<40)
Glucagon (pmol/l)	109 (<50)

In January 1989 the patient's parathyroid glands were removed and for technical reasons he also had a hemithyroidectomy. Subsequent histological examination showed hyperplasia of all four parathyroid glands. Postoperatively, results of tests of his thyroid function and his serum calcium concentration were maintained within the normal ranges by 150 µg thyroxine and 1 µg alfacalcidol daily. Despite the introduction of ranitidine 300 mg twice daily and a normal serum calcium concentration he continued to complain of abdominal pain. Ranitidine was therefore withdrawn and omeprazole (a long acting proton pump inhibitor) 40 mg twice daily was started, with good relief of his pain.

In June 1989 the patient was readmitted. His serum calcium concentration and results of tests of thyroid function were within the normal ranges and his renal function was stable (creatinine concentration 356 µmol/l). His serum gastrin concentration, however, was greatly increased at >400 pmol/l; this could have been partly due to omeprazole, which increases plasma gastrin concentration in half of patients with gastrinomas.⁴ At laparotomy a single 1.5 cm adenoma in the pancreas was resected. The rest of the pancreas, the liver, and the duodenum appeared normal.

Histological and histochemical examination of the resected adenoma showed positive staining for chromogranin A and neurone specific enolase, both recognised as markers of tumours of islet cells.⁵ Large amounts of glucagon were stored in the tumour (fig 1), and the pattern of granule storage on electron microscopy was consistent with a glucagonoma (fig 2). No positive staining for gastrin was shown. In situ

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FIG 1—Section of gastrinoma showing positive argyrophilic silver impregnation and indicating highly granulated nature of tumour cells. (Inset) detail of similar section immunostained for glucagon

FIG 2—Electronmicrograph of gastrinoma showing many granules with dense eccentric core. (Inset) granules stained for glucagon with immunogold technique

hybridisation to detect gastrin messenger RNA showed weak specific hybridisation in the tumour cells.

Nine months after the operation the patient remained well with stable renal function. Omeprazole was withdrawn postoperatively, and his plasma gastrin and glucagon concentrations fell to and remained within the normal range.

Comment

Multiple pancreatic adenomas are common in patients with the multiple endocrine neoplasia type I syndrome and may vary greatly in size.¹ Removal of one or more lesions detected by computed tomography, angiography, or laparotomy does not guarantee that the associated increased hormone concentrations will fall and thereby alleviate clinical symptoms. Roughly 30-40% of gastrinomas, whether sporadic or associated with multiple endocrine neoplasia type I, are also extrapancreatic (usually in the first or second part of the duodenum).⁶ Gastrinomas associated with multiple endocrine neoplasia type I are malignant in over 60% of cases,⁷ but there is evidence that duodenal gastrinomas, which are usually less than 2 mm in diameter, are less malignant and invasive than pancreatic ones,⁸ though this is disputed.³ Duodenal gastrinomas must be accurately located if surgical cure is to be successful. Routine venous sampling for gastrin before the operation has been advocated,⁸ and, if indicated, the duodenum should be opened, everted, and examined under an operating microscope to increase the chance of localising the tumour.

This case was further complicated by the concurrence of chronic renal failure, which provided an alternative explanation for the increased plasma gastrin and glucagon concentrations. The postoperative blood samples, however, showed that the gastrin and glucagon concentrations returned to normal after resection despite the persisting impairment of renal function.

Interestingly, the tumour stored and secreted glucagon yet did not store large amounts of gastrin. In the nine months after the pancreatic lesion was resected

the plasma gastrin and glucagon concentrations remained within the normal ranges (concurring with the results of the in situ hybridisation), indicating that the pancreas was producing gastrin ectopically. Before in situ hybridisation techniques were developed the source of gastrin secretion could not have been localised.

Discussion

SRB: Malignant duodenal gastrinomas may be more common than previously recognised. It is therefore important that when a gastrinoma is suspected the duodenum is also carefully investigated. Unfortunately, as duodenal gastrinomas are often less than 2 mm in diameter gastroscopy, even in combination with ultrasonography, is unlikely to show the lesion, thus emphasising the need for localisation before the operation. Total pancreatectomy has been advocated when multiple endocrine neoplasia type I is associated with multiple pancreatic adenomas. This, however, is a hazardous operation with a high mortality and morbidity as well as making the patient dependent on insulin and supplements of pancreatic enzymes for life. The unknown incidence of micrometastases is further reason to question the value of this operative approach.

JL: Norman Thompson at Ann Arbor is the only surgeon I am aware of who routinely opens and everts the duodenum to localise and thus remove duodenal gastrinomas.

DW: The published data from Ann Arbor are impressive: they show an 80% localisation rate and apparent cure (that is, normal plasma gastrin concentrations and no drug treatment) in over three quarters of patients at five years.

SRB: It is interesting that gastrin messenger RNA could be shown in the tumour but not storage of gastrin itself. This would imply hormone synthesis but some failure in the cellular storage mechanism. This is also seen in oat cell tumours of the lung, which often secrete, but do not store, various peptides.

CTD: What is the stability of gastrin messenger RNA, and is it possible that incorrect tumour fixation or storage could degrade the messenger RNA so that it would not hybridise under the conditions used?

JMP: Degradation does occur, which may give a higher background hybridisation or abolish specific hybridisation, thus emphasising the need for fresh tissue, snap frozen in liquid nitrogen.

SRB: Many tumours produce a considerable heterogeneity of messenger RNA sizes, which may further complicate studies on gene expression. Northern blotting as well as in situ hybridisation is useful if sufficient tumour is available.

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