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REVIEW ARTICLE

ENDOCRINE TUMOURS OF THE PANCREAS: REVIEW AND RECENT ADVANCES

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Pancreatic endocrine tumours (PET) are rare but nonetheless important to recognize and treat in a timely fashion. Significant morbidity occurs due to excess secretion of hormones, with all of the PET having some degree of malignant potential. Surgeons must plan directed operative strategies to deal with these tumours and be prepared to undertake aggressive palliative debulking resections if indicated. Somatostatin receptor scintigraphy and endoscopic ultrasound have been particularly helpful in both localizing and staging patients with PET. Other important advances in management include the use of long-acting somatostatin analogues to inhibit hormonal secretion and tumour growth. The possibility of multiple endocrine neoplasia type 1 (MEN-1) should be considered in any patient with a PET. The present article will review the various classes of PET, describe MEN-1 in relation to PET and examine advances in imaging and localization. The role of surgery for PET is also discussed in the present review.

Key words: endoscopic ultrasound, multiple endocrine neoplasia-1, pancreatic endocrine tumours, review, somatostatin receptor scintigraphy.

INTRODUCTION

Pancreatic endocrine tumours (PET) constitute a group of various rare lesions occurring in five per million people per year, with few surgeons experienced in their management. These tumours are challenging on two fronts: treatment must be directed first at the clinical syndrome caused by excess hormone production; and second, to the tumour itself and possibility of malignancy. The tumours are named according to the hormones they produce (Table 1). Although this group of diseases is termed PET, this can be misleading because many of the tumours occur outside the pancreas (e.g. gastrinoma; vasoactive intestinal polypeptide-secreting tumour (VIPoma); growth hormone-releasing hormone-producing tumour (GHRHoma); adrenocorticotropic hormone-producing tumour (ACTHoma); somatostatinoma). Tumours can occur in either sporadic fashion or in a hereditary fashion (multiple endocrine neoplasia (MEN)-1). In the present article, the PET and MEN-1 will be reviewed, and new advances in the area of imaging and treatment will be discussed.

INSULINOMA

The most common endocrine tumour of the pancreas is the insulinoma, occurring in approximately one new case per million population per year. Insulinomas synthesize and secrete insulin autonomously in the presence of low blood glucose levels, resulting in hypoglycaemia. Hypoglycaemic-induced catecholamine surge symptoms include tremor, irritability, weakness, tachycardia and hunger. Neuroglycopenic symptoms include bizarre behaviour, seizures, speech disturbances and coma. Relief of symptoms can be achieved by consumption of carbohydrate-rich foods. The first exploration for malignant insulinoma was undertaken by Dr W. J. Mayo and reported the following year by Wilder *et al.* in 1927.[1] Whipple's triad, associated with an insulinoma, consists of (i) hypoglycaemic symptoms while fasting; (ii) a blood glucose level < 50 mg/100 mL (2.8 mmol/L); and (iii) relief of symptoms following administration of glucose.[2]

Monitoring the insulin/glucose ratio, initially by an overnight fast, usually confirms the diagnosis. If the insulin/glucose ratio is > 0.3 (μU of insulin per mL/mg% glucose) this is diagnostic. If this is normal, a prolonged fast under medical supervision, for up to 72 h, is undertaken. Samples are drawn every 4–6 h during the fast, or whenever symptoms occur. C-peptide levels > 1.7 ng/mL and proinsulin levels $> 30\%$ also help confirm the diagnosis when factitious hypoglycaemia is suspected. C-peptide and insulin are the metabolic products of proinsulin cleavage within the β cells. After endogenous hypersecretion of insulin the levels of C-peptide and proinsulin should be high, unlike that after exogenous insulin preparations, when levels remain low.

Up to 90% of insulinomas are benign solitary tumours suitable for surgical resection or enucleation, whereas malignancy is present in only 5–10% of cases.[3]

Insulinomas are distributed evenly throughout the pancreas in the head, body and tail. Islet tumours that are multiple (MEN-1) or larger ones in the distal gland are resected by distal pancreatectomy. Smaller tumours not in direct approximation to the pancreatic duct can be enucleated. A tumour in the proximal pancreas is excised by enucleation with incision in the parenchyma made parallel to the pancreatic duct to avoid duct injuries. Rarely, large benign lesions in the head may be too large to safely enucleate so they should be treated by pancreaticoduodenectomy. In malignant insulinomas, resection of the primary and any accessible metastases should be undertaken. Tumours of the body/tail may be resected by a distal pancreatectomy and splenectomy including lymph nodes. Intraoperative insulin measurements have proved useful for predicting the completeness of surgery in patients

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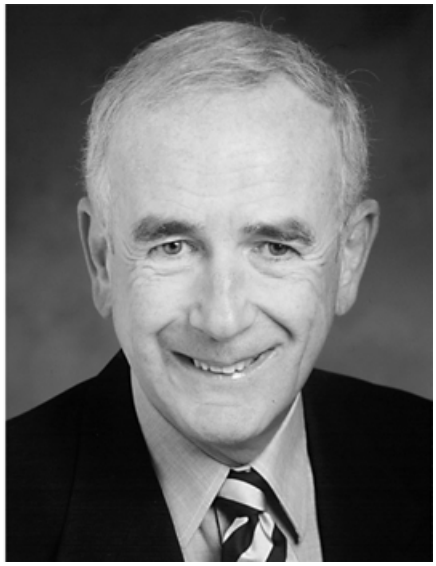

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with insulinomas.[4] Debulking of unresectable tumours can help alleviate hypoglycaemic symptoms.

Medical treatment (diazoxide) can help improve hypoglycaemic symptoms. Adjuvant chemotherapy (streptozotocin and 5-fluorouracil (5-FU)) and inhibition of tumour secretion by synthetic somatostatin analogues (e.g. octreotide, lanreotide) can help in patients with unresectable disease. Unfortunately only approximately 50% of insulinomas respond to octreotide, lacking somatotstatin receptors.

Misdiagnosis of insulinoma might occur in patients with adult pancreatic nesidioblastosis. This rare disease causes hyperinsulinaemic hypoglycaemia with clinical and biochemical features identical to those of insulinoma[5] but neither localization studies nor exploratory laparotomy for insulinoma reveal a discrete neoplastic lesion. Histopathology reveals the diagnosis of diffuse hyperplasia of the islet cells. For this diagnosis to be established preoperatively, selective pancreatic arterial stimulation with calcium and hepatic venous sampling for insulin is required (multiple high insulin levels). We use this test only when endoscopic ultrasound (EUS) fails to localize an insulinoma, which currently occurs in fewer than 10% of cases.

GASTRINOMA (ZOLLINGER–ELLISON SYNDROME)

Gastrinoma is the second most common islet cell secretory tumour, having an incidence of 0.5–1.5 per million population per year. In 1955 Zollinger and Ellison described a triad of (i) presence of primary peptic ulcerations in unusual locations; (ii) excess gastric secretions; and (iii) presence of an islet cell tumour of the pancreas.[6] This report preceded the discovery of gastrin, a polypeptide hormone and potent acid secretagogue that causes the Zollinger–Ellison syndrome (ZES).[7] A total of 25% of gastrinomas occurs in the presence of MEN–1 syndrome. Any patient suspected of having a gastrinoma should have serum calcium, parathyroid and prolactin levels measured, even when there is no family history of MEN-1.

The cause of this syndrome is hypersecretion of gastrin, resulting in peptic ulceration of the upper gastrointestinal tract. Gastrinoma should be suspected in any patient with peptic ulcer disease who does not respond to conventional treatment, or in patients with ulcer disease and severe diarrhoea. Abdominal pain and weight loss are common symptoms.

Fasting serum gastrin levels > 200 pg/mL are highly suggestive of gastrinoma and a value > 1000 pg/mL is diagnostic in the absence of achlorydria. Increased gastrin levels alone, however, are not sufficient, and other states (both ulcerogenic and non-ulcerogenic) cause hypergastrinaemia (Table 2).

Gastric acid analysis allows differentiation between ulcerogenic and non-ulcerogenic states. If the basal acid output is > 15 mEq/h, a diagnosis of gastrinoma is supported. Provocation testing with intravenous secretin causes a paradoxical stimulation of gastrin in patients with gastrinomas and is the most reliable diagnostic test (although secretin may be difficult to

Table 1. Pancreatic endocrine tumours

Tumour type	Hormone produced	Incidence (new cases per 10^6 per year)	Pancreatic location (%)	Duodenal location (%)	Other sites (%)	% malignant	Associated with MEN-1	Signs and symptoms
Insulinoma	Insulin	1–2	> 99			< 10	4–5	Hypoglycaemic, bizarre behaviour, coma
Glucagonoma	Glucagon	0.01–0.1	100			50–80	1–20	Weight loss, diabetes, rash
VIPoma	Vasoactive intestinal polypeptide	0.05–0.2	90		10% neural, adrenal, duodenal	40–70	6	Diarrhoea, hypokalaemia, hypochlorhydria, lethargy
Somatostatinoma	Somatotstatin	Unknown	55	45 (duodenal/jejunal)		70	45	Diabetes, gallstones, weight loss, steatorrhoea
Gastrinoma	Gastrin	0.5–1.5	25	70	5	60–90	20–25	Peptic ulceration, weight loss, steatorrhoea
GHRHoma	Growth hormone-releasing hormone	Unknown	30		7 (jejunal) 54 (lung) 13 (other)	60	16	Acromegaly
ACTHoma	Adrenocorticotropic hormone	Unknown	100			> 95	Rare	Cushing's syndrome
PPoma/non-functional	Pancreatic polypeptide	1–2	100			> 60	18–44	Abdominal pain, GI bleeds,diarrhoea

MEN, multiple endocrine neoplasia; GI, gastrointestinal; pop., population.

Table 2. Disease states associated with hypergastrinaemia

Ulcerogenic (hyperchlorhydric)	Non-ulcerogenic (non-hyperchlorhydric)
Gastrinoma	Post-vagotomy
Retained excluded antrum	Pernicious anaemia
Gastric outlet obstruction	Atrophic gastritis
Antral G cell hyperplasia/hyperfunction	Short gut syndrome
	Renal failure

obtain). Once 2 U/kg of secretin is given, serum samples for gastrin are taken for up to 30 min. Gastrinoma is diagnosed if gastrin levels increase 200 pg/mL over the baseline level. If patients are already on H+–K+ adenosine triphosphatase (ATPase) inhibitors, the drug should be stopped for 5 days before gastrin levels are measured.

Preoperatively all patients should receive H+–K+ ATPase inhibitors (omperazole/lansoprazole/pantoprazole) to treat the gastric acid hypersecretion (also known as proton pump inhibitors).

All patients with ZES without liver metastases are considered operative candidates for a curative procedure. Preoperatively, staging and localization are accomplished by computed tomography (CT) scan, octreotide scan and EUS. Most gastrinomas are found in the gastrinoma triangle which includes the pancreatic head, uncinate and duodenum. If the patient has sporadic ZES with no evidence of a pancreatic tumour after thorough evaluation, a duodenotomy is performed because microgastrinomas may be the sole cause of the hypergastrinaemia.[8] The majority of patients with sporadic ZES have been found to have duodenal primary rather than pancreatic tumours, most of which cannot be identified by preoperative localization studies.

A 6-cm longitudinal incision is made in the second part of the duodenum, allowing digital evaluation from the antrum to the fourth part of the dudodeum. If no submucosal tumour is palpable, the mucosa is everted and palpated in a meticulous circumferential fashion to detect tumours as small as 1–2 mm underneath the mucosa. Tumours < 4 mm are excised locally but tumours 5 mm or larger are removed with a full thickness ellipse of the duodenum and a margin around the tumour.[9] We routinely perform a peripancreatic lymph node dissection including nodes in the porta hepatis and along the common hepatic artery in patients with duodenal tumours or when a pancreatic tumour is 3 cm or larger. A whipple resection for ZES patients with localized disease is not advocated when both the primary and involved nodes can be removed by a lesser procedure, such as enucleation.

If, despite extensive searching, no primary tumour is found, several options remain: first, closure without intervention, other than peripancreatic lymph node dissection, if the patient has controlled acid hypersecretion; and second, parietal cell vagotomy. Cholecystectomy should be performed due to the possibility of future unresectable disease amenable to treatment with somatotstatin analogues that cause cholestasis and cholelithiasis. Unresectable tumours can also be treated with chemotherapy (doxorubicin; 5-FU; streptozocin). Antisecretory medication should be continued indefinitely. Subsequent to the recognition that occult duodenal tumours and lymph node metastases were the most common aetiology of sporadic ZES, negative explorations dramatically decreased and are now rare.

GLUCAGONOMA

The glucagonoma syndrome, caused by excess glucagon secretion, is associated with mild diabetes mellitus and a severe dermatitis (necrolytic migratory erythema). The rash is typically located on the lower abdomen, perineum and lower extremities. Other symptoms include anaemia, malnutrition, glossitis, weight loss, venous thrombosis and neuropsychiatric manifestations. Glucagon excess enhances hepatic conversion of amino acid nitrogen into urea nitrogen, resulting in low blood amino acid levels.

Diagnosis is made when plasma glucagon levels are elevated; usually > 500 pg/mL, with normal values being < 120 pg/mL.

Preoperatively the diabetes should be optimized and necrolytic migratory erythema treated. All patients should be given subcuticular heparin cover due to the increased risk of thrombosis. Treatment with octreotide can reverse the catabolic effects of glucagon excess and adequately prepares even the most unfavourable patient for operation.

Most glucagonomas are malignant; metastases have been found in 80% of patients with glucagonomas, and complete resection is possible in only 30%. The majority of the tumours originate in the body and tail and tend to be large at time of exploration. Chemotheraputic treatment with 5-FU and streptozotocin as well as dacarbazine (DTIC) have reported to help incurable or recurrent disease.[10] Octreotide may help control hyperglycaemia and skin lesions. Hepatic embolization is the best form of non-operative palliative treatment.[11] The 5-year survival rate is 50%.[12] In patients with smaller glucagonomas, usually detected incidentally by CT scans and without the syndrome, the results of resection for cure are much more favourable.

VIPOMA (VERNER–MORRISON SYNDROME)

This syndrome has many names including the Verner–Morrison Syndrome, WDHA (watery diarrhoea; hypokalaemia and either achlorhydria or hypochlorhydria); and pancreatic cholera. Patients present with large amounts of watery diarrhoea, averaging 3 L per day. The diarrhoea contains excess potassium and bicarbonate leading to a hypokalaemic acidosis. Patients are often lethargic, and nauseated with muscular weakness. Other symptoms that have been attributed to this syndrome include hypercalcaemia and hyperglycaemia with cutaneous flushing observed in a minority.

Diagnosis is confirmed by elevated VIP levels of approximately 1000 pg/mL (normal: 0–75 pg/mL). The VIP secretion is episodic so several fasting values may need to be measured.

Preoperatively fluid and electrolyte abnormalities are corrected and octreotide used to decrease VIP levels, reducing diarrhoea.

Definitive treatment is surgical excision of the tumour. Because most VIPomas are in the distal pancreas, distal pancreatic resection is performed. If no pancreatic tumour is found then the retroperitoneum and adrenals should be thoroughly examined for tumour. Fifty per cent of cases have metastases at presentation and treatment involves palliative debulking. Octreotide and indomethacin are useful in patients with unresectable tumours for symptomatic control. The combination of streptozocin and 5-FU provides tumour response rates of > 50%.[13] Of all the functional PET, VIPomas appear to be most responsive to octreotide. In some cases the use of octreotide may result in tumour necrosis and long-term inhibition of metastatic growth. In patients explored with metastatic disease, the gall bladder should be routinely excised in anticipation of the use of long-acting octreotide.

SOMATOSTATINOMA

The somatostatinoma syndrome occurs in less than 1 in 40 million people. Symptoms are non-specific and are caused by somatostatin's ability to inhibit the function of most of the digestive organs. Symptoms include steatorrhoea, diabetes, hypochlorhydria and cholelithiasis. Diagnosis is confirmed by finding raised levels of plasma somatostatin, often > 10 ng/mL (normal: 10–50 pg/mL).

Preoperatively, treatment of hyperglycaemia and malnutrition should be addressed. Most somatostatinomas have been located in the head of the pancreas and periampullary region. Surgical treatment involves resection of the primary and usually debulking hepatic metastases. Cholecystectomy is indicated due to the high incidence of gallstones with continuing hypersomatostatinaemia.

The prognosis of advanced metastasizing somatostatinomas is poor and average survival is < 24 months.[14]

GHRHOMA

Growth hormone-releasing hormone (GHRH) from the pancreas or other site (lung/gastrointestinal tract) causes the normal pituitary to release enhanced amounts of growth hormone leading to acromegaly. The sella is normal in size and magnetic resonance imaging (MRI) and CT scans of the pituitary are also normal. Many of these tumours express somatostatin receptors on the cell surface, making treatment with octreotide possible.[15] The ideal therapeutic procedure is complete surgical resection of the lesion but if metastases have occurred, debulking is important to decrease GHRH stimulation on the pituitary.[11]

ACTHOMA

Pancreatic ACTHomas account for 4–16% of all ectopic Cushing's syndrome. Because 96% of these PET are malignant, the abdomen should be carefully imaged to look for a liver metastasis or pancreatic mass. If none are present then the likelihood of a pancreatic ACTHoma being the cause of ectopic ACTH is very unlikely. The ACTHoma can occur in conjunction with malignant gastrinoma. Pancreatic endocrine tumours that secrete both gastrin and either CRF or ACTH are invariably aggressive tumours and are associated with a poor prognosis.

PPOMA

Pancreatic polypeptide (PP) is a hormone secreted by pancreatic endocrine cells in response to food, but its function is not completely understood. Pancreatic polypeptide is frequently secreted by other PET so in order to classify a tumour as a PPoma more than 50% of PP-secreting cells must be identified by immunohistochemistry.[16] PPomas are associated with minimal or non-specific clinical manifestations, or no clinical endocrine syndromes. Patients present with weight loss, jaundice and abdominal pain due to the mass effect of the tumour (Figs 1–3). The diagnosis can be established by measuring fasting circulating levels of PP: values > 300 pg/mL are diagnostic.

Surgical resection is the treatment of choice; debulking of large tumours relieves mass effects and malignant behaviour.

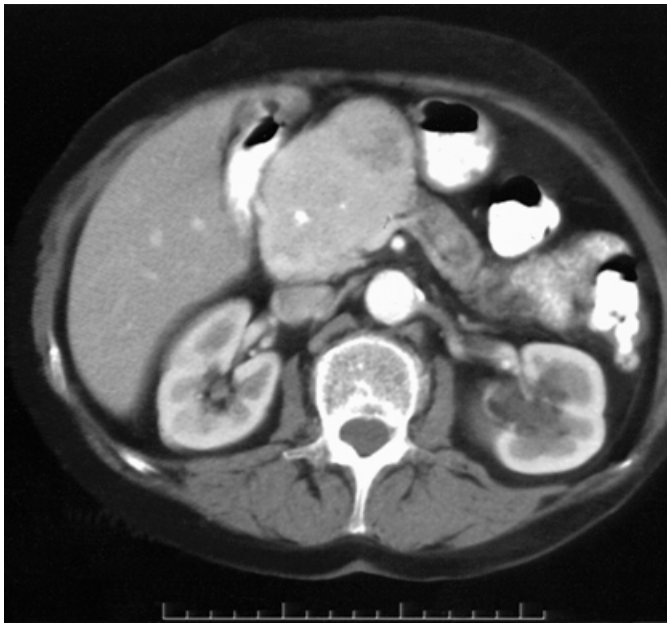

Fig. 1. A 6 × 8-cm pancreatic head mass revealed by computed tomography scanning in an asymptomatic patient. This was a non-functioning pancreatic endocrine tumour producing pancreatic polypeptide at 1600 pg/mL (normal: 0–300 pg/mL).

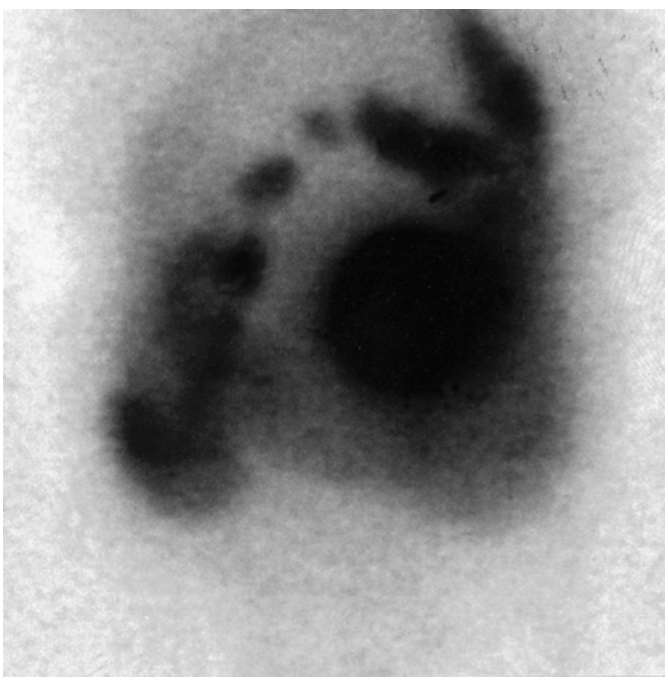

Fig. 2. Indium 111 octreoscan showing marked uptake in the pancreatic head tumour. There is normal tracer uptake by the liver, spleen and kidney. Normal excretion of radioactivity into the gut is seen.

Chemotherapy with streptozotocin and somatostatin analogues to treat residual disease have both been used.[16,17]

Non-functioning pancreatic endocrine tumours

Non functioning PET are not associated with a specific clinical syndrome. This can occur if the tumour does not secrete enough

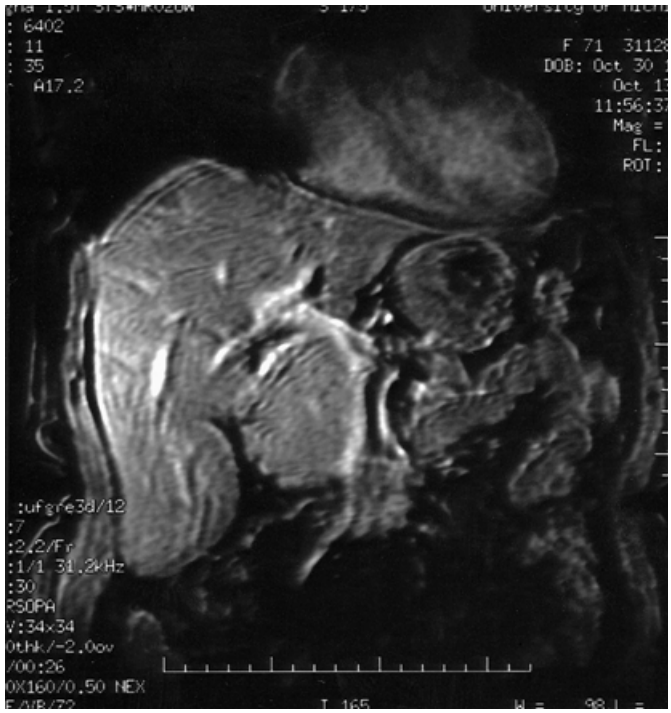

Fig. 3. Axial 3-D magnetic resonance imaging scan showing the pancreatic polypeptide-producing tumour in the head of the pancreas.

hormone to produce a clinical syndrome or if the hormone secreted causes no specific symptoms (e.g. PPoma). These tumours present late, often with a palpable mass or with pressure symptoms and a high malignancy rate (90%). More than 60% of cases have liver metastases at the time of diagnosis. The lesion is commonly located in the head or neck of the pancreas. In some cases portal hypertension may result from superior mesenteric vein involvement. More recently, non-functioning PET have been detected incidentally with CT scans while still being resectable for cure based on staging with octreotide scanning. An aggressive surgical approach including resection and replacement of the superior mesenteric vein, if involved, is considered justified in selected cases. Incurable disease can be debulked, with surgical palliation of jaundice and gastric outlet obstruction by biliary enteric or gastroenteric bypass, respectively. Streptozocin and 5-FU have been used,[18] as has interferon.[19] Five-year survival rates for metastatic non-functioning PET averages 25–45%.[16]

Plasma chromogranin A is raised in 60–100% of both functional and non-functional PET. This peptide can be used in assessing tumour progression, relapse and tumour burden. Serum chromogranin levels have proven to be a non-imaging method to diagnose non-functional PET as well as to monitor recurrence.[20]

Multiple endocrine neoplasia 1

MEN–1 syndrome is an autosomal dominant disorder caused by germline mutations in the MEN-1 gene localized on chromosome 11q13.[21] Its clinical expression involves the pancreas (60–85%), parathyroids (85–100%), pituitary (40–70%) and adrenal cortex (20–40%). Patients generally present with primary hyperparathyroidism before pancreatic disease is

detected. Parathyroidectomy can be safely perfomed during the same anaesthetic if hyperparathyroidism has not previously been treated. Either a subtotal parathyroidectomy with a 60-mg remnant or a total parathyroidectomy with autotransplantation can be performed. Both should be accompanied by a cervical thymectomy.[22] Thymic carcinoids, usually in male patients, are a rare but potentially lethal manifestation of MEN-1 and are an indication for prophylactic thymectomy,[23] in addition to the need to excise supernumerary thymic parathyroids present in 15–20% of patients with MEN-1.

Multiple endocrine neoplasia-1 pancreatic disease is usually multicentric. Of the functional tumours, gastrinomas are most common, with the majority arising in the duodenum rather than in the pancreas, followed by insulinomas. Other hormones that may be secreted include VIP, glucagon, PP, calcitonin, or 5 hydroxytryptophan (carcinoid islet cell tumour). Since the development of effective drug therapy to control acid secretion, the management of gastrinomas in MEN-1 has become controversial. Some have recommended a non-operative approach using proton pump inhibitors to control symptoms because of a previously high failure rate to achieve surgical cure.[24,25] However we recommend surgical resection, despite the occurrence of multiple tumours and the propensity for recurrence, to reduce the risk of metastases.[26] Once it was recognized that MEN-1 patients with ZES usually had one or more duodenal gastrinomas, frequently with local nodal metastases, a surgical procedure addressing these tumours as well as those in the pancreas frequently was successful. Because neuroendocrine tumours of the pancreas and duodenum have malignant potential, the functional manifestations can actually be eliminated with an appropriate procedure. Provided that the tumour(s) have not metastasized to the liver and that the operation is extensive enough to excise all sites of disease, these patients can be cured. Our current operation in MEN-1 patients with ZES consists of distal pancreatectomy (invariably other PET present), enucleation of any head or uncinate PET, which may secrete gastrin (10–30%), duodenotomy with excision of one or more gastrinomas (always present) and peripancreatic lymph node dissection (metastatic nodes in 50%).

Surgical treatment of patients with insulinomas, glucagonomas, VIPomas and MEN-1 is generally advocated to obtain a cure, again provided that no distant metastases are present. The MEN-1 patients with hypoglycaemia have multiple insulinomas in the body and tail of the pancreas and are routinely treated by distal pancreatectomy with enucleation of any tumours in the head or uncinate. Duodenotomy is not performed unless the serum gastrin is elevated.

The likelihood of MEN-1 should be considered in any patients with a PET. The possibility of and the need to detect other endocrinopathies should be addressed. From a practical viewpoint only a serum calcium test and prolactin test need to be done routinely. Genetic testing is available and family members should be screened if other endocrine tumours are found or the family history is positive. As genetic testing becomes more available, it will be feasible to perform a simple, inexpensive reliable test on all PET patients.

IMAGING AND LOCALIZATION

Dynamic contrast abdominal computed tomographic (CT) scanning with intravenous and oral contrast is recommended as a baseline imaging technique for localizing and staging PET. Potential liver metastases and peripancreatic lymph node enlargement should be ruled out. Magnetic resonance imaging may also be useful, particularly in looking for metastases[27,28] and in delineating the relationship of the mass to the pancreatic duct and major vessels (Figs 4,5).

Somatostatin receptor scintigraphy (SRS or octreotide scanning) with radiolabelled octreotide has proven to be a sensitive localization tool and is now used routinely in staging patients with PET. It will detect most primary tumours or metastases 1 cm or larger. This technique relies on the fact that many PET possess high densities of somatostatin receptors, thus identifying primary tumours as well as hepatic and extrahepatic metas-

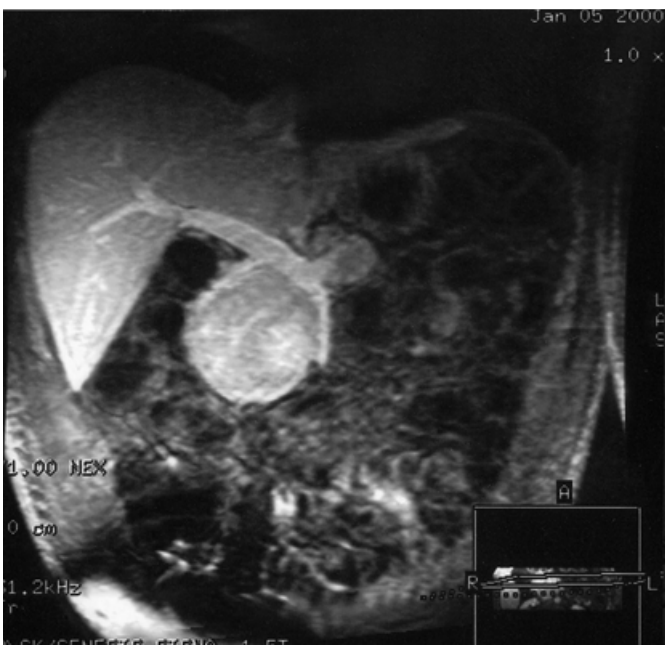

Fig. 4. Magnetic resonance imaging scan. Axial T2 image demonstrating a massive vasoactive intestinal polypeptide (VIP)-secreting tumour found in a 41-year-old man who presented with profuse secretory diarrhoea and a VIP level of 1460 pg/mL (normal: 0–75 pg/mL).

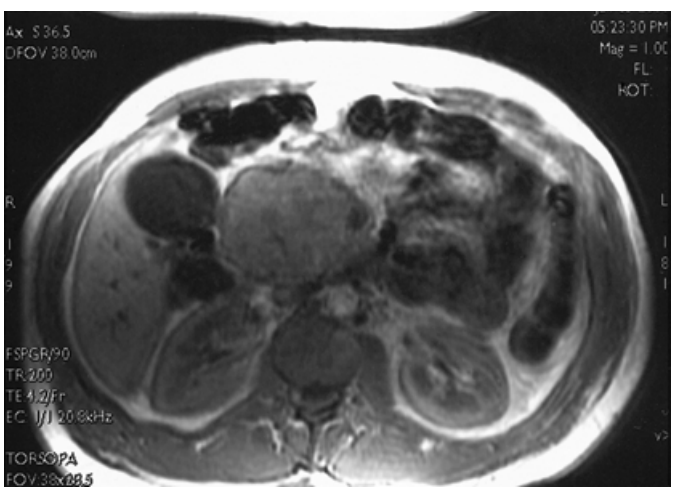

Fig. 5. Magnetic resonance imaging scan. Coronal T1 image demonstrates the vasoactive intestinal polypeptide (VIP)-secreting tumour (8.5 cm) within the head and neck of the pancreas. There is displacement of the portal vein/superior mesenteric veins, but both remain patent.

tases.[29,30] Somatostatin receptor scintigraphy allows for whole-body assessment specific for neuroendocrine tumours that may be significant for identifying extraduodenopancreatic disease. The National Institutes of Health group determined that SRS was the single most sensitive test for localizing both primary and metastatic gastrinomas.[29] In a study of 151 patients with gastrinoma, SRS detected 79% of sporadic gastrinomas and 91% of MEN-1 gastrinomas.[31] Our experience has been that most sporadic duodenal gastrinomas are not localized by octreotide because of their small size and that metastatic nodes are much more likely to be the source of the positive study. The positive studies in MEN-1 patients are usually from the pancreatic PET. Somatostatin receptor scintigraphy uptake is significantly less frequent in insulinomas whereas EUS is much more sensitive for insulinomas.[32]

Endoscopic ultrasound has been shown by some groups to be more sensitive than CT or arteriography combined, but is dependent on operator experience as well as on the site and size of the neoplasm.[33] Its sensitivity for endocrine pancreatic tumours is higher than 75% and often reaches 90–100%. Endoscopic ultrasound is particularly good for detecting small PET in the head, uncinate and body of the pancreas. Although some have reported that 50% of duodenal gastrinomas are detected by EUS,[33,34] that has not been our experience. We have found that most patients with ZES and a duodenal gastrinoma have a negative EUS. The sensitivity of EUS for metastatic lymph nodes is approximately 58%.[35] If EUS detects an insulinoma, no other localization study is needed. It detects nearly all tumours 4 mm or larger within the pancreas. In sporadic gastrinoma patients a negative pancreatic EUS should rule out pancreatic localization because nearly all such tumours are 1 cm or larger. This contrasts to those in the duodenum, most of which are < 1 cm.

Intraoperative ultrasound (IOUS) can help visualize non-palpable intrapancreatic insulinomas and gastrinomas and their relationships to ducts and vessels. Smaller tumours in the duodenal wall and lymph nodes are not routinely detected because of the heterogenous sonographic background. A combination of IOUS and bimanual palpation by an experienced surgeon can achieve high detection rates of insulinomas[36,37] and should be done if the tumour remains occult after initial exploration.

Selective venous sampling (SVS) of the portal vein, although more sensitive (70–90%), is invasive, technically challenging,[38] expensive, potentially more morbid and often available in only a few centres. The tumour drains its hormonal products into the portal venous system causing a rise in concentration, thus regionalizing the neoplasm. It has been largely supplanted by hepatic venous sampling after selective arterial stimulation.

Selective pancreatic arterial stimulation with hepatic venous sampling (Imamura Test) evaluates the appropriate hormone levels after selected stimuli are injected at the time of pancreatic arteriography. This technique does not localize tumours, rather regionalizes the hypersecretion. Small doses of secretin or calcium are injected sequentially into the superior mesenteric, gastroduodenal and splenic arteries, with blood samples collected from the hepatic vein. An increase in the level of gastrin following secretin administration regionalizes a gastrinoma. An increase in the level of insulin following calcium is indicative of an insulinoma. In combination with intraoperative ultrasound this can enhance surgical success.[39]

Selective pancreatic angiography is rarely used by itself, but may be valuable when EUS is negative. A hypervascular blush is seen around the tumour. This technique depends on the expertise of the radiologist as well as on the size and neovascularity of the primary tumour. Because angiography demonstrates fewer than 40% of insulinomas and gastrinomas,[40] it is currently used only in conjunction with selective arterial stimulation tests.

FOLLOW UP

Patients with PET need regular long-term follow up for recurrence of tumour or metastases. Benign sporadic insulinoma patients are the exception because they are generally cured by surgical resection. Other patients with sporadic functional tumours require annual specific hormone studies even if asymptomatic. The MEN-1 patients need annual follow-up hormone studies and periodic imaging with CT and octreotide scans. We currently recommend EUS of the remaining pancreatic head even in the asymptomatic patient. Recurrence should be aggressively managed by re-resection or chemotherapy as dictated by the original operation, tumour type and extent of recurrence.

CONCLUSIONS

Pancreatic endocrine tumours include a group of fascinating functional tumours as well as a significant group without apparent hormonal manifestations that are difficult to diagnose until they are advanced locally or associated with liver or distant metastases. Once the diagnosis has been made, surgical difficulties can beset the most experienced of endocrine surgeons. These include localization, function neutralization, extent of resection, treatment of liver metastases and appropriate chemotherapy. Regrettably there is a paucity of prospective randomized trials on which to establish appropriate ‘evidence-based surgery’. Although rare, it is important for the general surgeon to be aware of these tumours and be able to diagnose and treat appropriately. There is increasing evidence that with earlier diagnosis, improved localization or directed operative strategy (duodenotomy for occult gastrinoma), lymphadenectomy when appropriate, extensive palliative resections, use of long-acting somatostatin analogues to inhibit hormonal secretion and tumour growth, and embolization or ablation of liver metastases, that the long-term results have improved during the past two decades.

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