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Basic Science and Clinical Management

With 82 Figures

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Neuroendocrine Tumours

4 GI Hormone Producing Tumours: Syndromes and Treatment Options

Mary McStay and Martyn E. Caplin

Neuroendocrine tumours of the pancreas (also called pancreatic endocrine tumours or islet cell tumours) may be *functioning* or *non-functioning*. Functioning tumours are those associated with a clinical syndrome that is caused by hormone release, and are named according to the hormone that they secrete (Table 4.1). Non-functioning neuroendocrine tumours of the pancreas include those that have all the histological characteristics of a neuroendocrine pancreatic tumour (NPT), but no associated clinical syndrome related to hormone hypersecretion. NPTs are rare tumours, with an incidence of less than 1/100 000 population/year. Non-functioning tumours form the biggest group (30–40%), followed by gastrinomas and insulinomas, which have approximately the same incidence. With the exception of insulinomas, the majority of NPTs are malignant.

Eight of the NPTs are well established and are included in most classifications. These are gastrinomas, insulinomas, VIPomas, glucagonomas, somatostatinomas, growth-hormone releasing factor secreting tumours (GRFomas), ACTH secreting tumours of the pancreas (ACTHomas), and 'non-functioning' tumours, which may in fact be pancreatic polypeptide-secreting tumours (PPomas). Other rarer NPTs have recently been considered as causing syndromes, including NPTs causing hypercalcaemia (producing parathyroid hormone and parathyroid hormone-related protein), NPTs secreting calcitonin and NPTs causing the carcinoid syndrome.

Pathophysiology and Pathology of Neuroendocrine Tumours

The histological diagnosis of neuroendocrine tumours relies first on the identification of general markers of neuroendocrine differentiation, and then cell-specific characterisation. Neuroendocrine differentiation is evaluated by immunohistochemistry using antibodies against secretory granule proteins (chromogranin A, synaptophysin) and cytosolic proteins (neuron-specific enolase, protein gene product 9.5). The cell-specific characterization of neuroendocrine tumours requires hormone immunohistochemistry. According to the World Health Organisation (WHO) classification, neuroendocrine tumours of the gastroenteropancreatic tract are classified as well-differentiated and poorly differentiated depending on their histological and functional features.

Table 4.1. The different types of pancreatic neuroendocrine tumours and their associated hyperfunctional syndromes

Tumour	Cell type	Predominant hormone	Major clinical symptoms	Tumour location	Percent malignant
Gastrinomas	G	Gastrin	Recurrent peptic ulcer	Pancreas 50% Duodenum 50%	90
Insulinoma	B	Insulin	Hypoglycaemia (fasting or nocturnal)	Pancreas	10
VIPoma	?	Vasoactive intestinal polypeptide (VIP)	Watery diarrhoea, hypokalaemia, achlorhydria	Pancreas 90%	60
Glucagonoma	A	Glucagon	Diabetes mellitus, necrolytic migratory erythema	Pancreas	90
Somatostatinoma	D	Somatostatin	Diabetes mellitus	Pancreas 55% Duodenum 45%	80
GRFoma	?	Growth-hormone releasing-hormone	Acromegaly	Pancreas 30% Lung 50% Jejunum 15%	60
ACTHoma	?	ACTH	Cushing's syndrome	Pancreas 90%	95
PPoma	PP/F	Pancreatic polypeptide (PP)	Hepatomegaly, abdominal pain	Pancreas 100%	80

Well-differentiated tumours are positive for most markers of neuroendocrine differentiation in the vast majority of tumour cells. Poorly differentiated tumours do not express chromogranin A, but retain cytosolic markers together with synaptophysin. Other helpful features used to classify these tumours, and therefore to attempt to gauge their behaviour, include general morphologic description; mitotic rate (two or more mitoses per 10 high power [×400] microscopic fields); proliferative index (as assessed by nuclear Ki67 expression); tumour size; evidence of invasion of blood vessels, nerves, or adjacent organs by the neoplasm; predominant tumour synthesis of a specific hormone; or complete non-functionality of the tumour at an immunohistological level. Well-differentiated tumours are then named according to the specific endocrine cell of which they are composed (usually the cell types normally observed in the anatomical site of the tumour). Tumours falling into the two major categories of well-differentiated and poorly differentiated exhibit significant differences in phenotype and behaviour. The behaviour of well-differentiated tumours can be unpredictable, varying from benign to low-grade malignant;[1] according to the several clinicopathological parameters mentioned above, a tentative risk class is assigned to the tumour. Poorly differentiated (small cell) endocrine carcinomas are highly aggressive and are associated with a poor prognosis.

MEN-1 Syndrome

The MEN-1 syndrome is most commonly associated with primary hyperparathyroidism, and tumours of the endocrine pancreas and anterior pituitary.

This autosomal dominant inherited syndrome is associated with a germline genetic mutation in the MEN1 gene, on chromosome 11.[1] Genetic mapping studies show somatic loss of heterozygosity (LOH) suggesting that development of MEN1 associated tumours is a two-step process: firstly, a germline mutation affecting the first MEN1 allele; and then a somatic inactivation of the unaffected allele by LOH.[1,2] The MEN1 gene was cloned in 1997[3,4] and encodes a 610 amino acid protein called menin. Menin is a putative growth-suppressor protein, which specifically binds JunD, a transcription factor acting through the activator protein-1 (AP1 complex).[5] AP1 is a regulatory system within the cell, which is involved in a plethora of functions including apoptosis, mitosis and response to endogenous or exogenous growth factors.

Characteristically, hyperparathyroidism is the initial manisfestation of MEN-1, usually presenting in the third decade of life, and followed by the development of an NPT between the ages of 35 and 50 years. Recognition of MEN-1 is an important first step in the management of NPTs, because patients with and without MEN-1 differ in clinical presentation, clinical management approaches, and also prognosis. The presence of additional endocrinopathies may need specific management and may have an influence on the main tumour management. For example, in patients with gastrinoma and hyperparathyroidism, the presence of hypercalcaemia resulting from hyperparathyroidism often stimulates the release of gastrin from the tumour, and parathyroidectomy has to be performed before gastrinoma surgery. Patients with MEN-1 may develop multiple tumours simultaneously, and more than one type of NPT over time, thus the chances of surgical cure and the approach to long-term follow-up will differ from patients without

MEN-1. Additionally, screening of other family members of MEN-1 patients is indicated. Systematic biological screening performed on these patients includes: measurement of parathyroid hormone, serum calcium, prolactin, luteinising hormone, follicle stimulating hormone, growth hormone, adrenocorticotrophic hormone (ACTH), morning cortisol and 24 h urinary cortisol.

Other hereditary neoplasia syndromes associated with NPTs include neurofibromatosis type 1 and von Hippel-Lindau disease. Neurofibromatosis type 1 (NF1) is inherited in an autosomal dominant manner, arising from mutation of the NF1 gene. The NF1 gene is a tumor suppressor gene encoding a large protein (neurofibromin) that functions primarily as a RAS negative regulator.[6] The hallmark feature of NF1 is the presence of neurofibromas arising either in the dermis or in peripheral nerve. However, patients also have an increased incidence of other tumours, including phaeochromocytomas and duodenal tumours, including somatostatinomas. Clinically von Hippel-Lindau(VHL) disease displays an autosomal dominant pattern of inheritance. Germline mutation of the VHL tumour suppressor gene on chromosome 3 causes a hereditary cancer syndrome characterised by the development of retinal and central nervous system haemangioblastomas. Other tumours associated with VHL disease include clear cell renal carcinomas, phaechromocytomas, and neuroendocrine tumours of the pancreas.[7]

Clinical Syndromes of Neuroendocrine Tumours

Gastrinomas

Gastrinomas have an annual incidence of 0.5–1.5 per 10^6 persons,[8] the majority of the tumours are located either in the pancreas or the duodenum. Less frequent sites are the small intestine and the stomach.[9] Approximately 20% of patients have a family history of neuroendocrine tumours, and 20–25% of patients (particularly those with duodenal tumours) have the MEN1 syndrome. MEN-1-associated gastrinomas usually present at an earlier age, and most MEN-1 patients have coexisting hyperparathyroidism or pituitary disease at the time of presentation. As gastrin is trophic for the enterochromaffin cells in the fundus of the stomach (ECL cells), prolonged hypergastrinaemia may lead to the development of so-called ECLomas, which are also mostly benign neuroendocrine tumours.[10] ECLomas are more frequent in patients with MEN1-associated gastrinoma (15–30%) than in those with sporadic gastrinoma (<5%).

Gastrinomas manifest with the characteristic Zollinger–Ellison syndrome (ZES), which is caused by hypergastrinaemia associated with hypersecretion of gastric acid. The most common symptom is abdominal pain caused by *peptic ulceration*.[11] Ulcers are most commonly found in the first part of the duodenum (approximately 75%), and are usually single, but can be multiple. Ulcers are found much less often in the stomach, and in contrast to the common peptic ulcer, which is associated with *Helicobacter pylori* or ingestion of non-steroidal inflammatory drugs, may also by found in the second, third and fourth parts of the duodenum (14%), and in the jejunum (11%).[12] Ulcers are often recurrent and/or resistant to medical or surgical treatment.

Gastroesophageal reflux disease is also common. Approximately 60% of patients with Zollinger-Ellison Syndrome have dysphagia, or endoscopic evidence of erosive oesphagitis, including its complications of stricture formation, Barrett's

epithelium, and perforation.[13,14] A recently appreciated, important endoscopic sign is the presence of prominent endoscopic folds, which was present in 94% of patients in a large prospective series of patients.[11]

The other characteristic component of the syndrome is *diarrhoea*, which occurs in the majority of patients.[11] This is of the secretory or motor variety, and is always associated with hypersecretion of gastric acid, making it easily distinguishable from the diarrhoea associated with VIPomas, which is associated with hypochlorhydria.[15] The diarrhoea may accompany, precede or follow the peptic ulcer disease, or in some cases it may be the only manifestation. The large amounts of hydrochloric acid in the upper GI tract lowers the intraluminal pH, producing other effects: steatorrhoea, through the inactivation of pancreatic lipase, and the insolubilisation of some primary bile acids; vitamin B malabsorption, by interference with intrinsic factor-mediated vitamin B12 absorption by the distal ileum.[12]

An estimated 60% of gastrinomas run a malignant course. Approximately 50% of patients with pancreatic or duodenal gastrinomas have lymph node and/or liver metastases at presentation. For many years, the main causes of death among gastrinoma patients were the complications of peptic ulcer disease: perforation, haemorrhage and pyloric stenosis. However, with the advent of effective acid-reducing pharmacological agents, in particular proton pump inhibitors, the primary morbidity has changed to that of tumour growth and spread.

Insulinoma

Insulinomas have an annual incidence of $1–2/10^6$ persons/year, and usually occur in patients between 30 and 60 years of age. Insulinomas are small (81% measure 20 mm or less),[16] usually solitary, and are almost always confined to the pancreas. They are evenly distributed within the head, body and tail of the pancreas. Approximately 10% of the tumours are malignant tumours, these are usually larger than benign lesions, and can lead to widespread metastases. Multiple tumours occur in up to 10% of patients and should raise the possibility of MEN-I syndrome.

The tumour is characterised by hypersecretion of insulin and hypoglycaemia. Symptoms occur as the result of hypoglycaemia and characteristically occur when a meal is delayed or missed, with fasting, or during exercise.[17] Most patients present with neurological symptoms of hypoglycaemia, such as visual disturbances, altered mood/confusion, weakness, transient motor defects, fatigue, dizziness, and even coma. Hypoglycaemia can also cause symptoms of adrenergic hyperactivation, such as hunger, palpitations, sweating and tremor. When the diagnosis is made late, hypoglycaemia may even cause permanent cerebral damage. The symptoms can be partially masked by a tendency to over-eat in order to compensate for the hypoglycaemia. For this reason, insulinoma patients are often overweight.[18]

VIPoma

Vasoactive intestinal polypeptide (VIP)-secreting tumours (VIPomas) account for less than 10% of pancreatic neuroendocrine tumours. They are much more

common in women (with a female:male ratio of 3:1), and most frequently occur at around the fourth decade of life.[9] Up to 90% of VIPomas originate from the pancreas, and are usually solitary tumours. The remaining 10% are tumours of the nervous system, such as ganglioneuromas, neuroblastomas and phaeochromocytomas. Approximately 5% of VIPomas are MEN-1-associated. Over 60% of pancreatic VIPomas are malignant, and by the time of diagnosis up to 60% have metastasized to lymph nodes, liver, kidneys, or bone.[8,19]

The hypersecretion of VIP produces a syndrome characterised by severe secretory diarrhoea, associated with hypokalaemia and dehydration, and is commonly called the *Verner-Morrison Syndrome*. The diarrhoea is intermittent in 53% of patients, and continuous in 47%. The volume of diarrhoea is large, with the majority of patients having more than 3 l/day.[20] The pathogenesis of the severe hypokalaemia is probably primarily caused by faecal loss, and if left uncorrected may be severe enough to cause life-threatening cardiac arrthymias. Other electrolyte abnormalities include: hypochlorhydria, hypercalcaemia, hyperglycaemia, and hypomagnesaemia.[17] A less frequent symptom is cutaneous flushing, which is characteristically erythematous, and occurs in 20% of patients.

Glucagonomas

Glucagonomas are less than half as common as VIPomas, with an annual incidence of 0.01–0.1 new cases per million. They are slightly more common in women (55%), and usually occur after 45 years of age.[21] Most glucogonomas are large solitary tumours, which are almost exclusively found in the pancreas. They generally exhibit highly malignant behaviour: approximately 90% of patients already have lymph node and/or liver metastases at presentation.[8] Glucagonoma is rarely associated with MEN-1.

Glucagonomas secrete excessive amounts of glucagon and cause a distinct syndrome that is characterized by a specific dermatitis (*necrolytic migratory erythema*), weight loss, diabetes mellitus, and anaemia. The cutaneous lesions are one of the most common manifestations of the disease, being present in about 90% of patients. Characteristically, the skin lesion starts as an erythematous area that subsequently becomes papular, with superficial blistering that frequently erodes and crusts. Healing is associated with hyperpigmentation of the area involved. The eruption is usually localized to the buttocks, groin, perineum, elbows, hands, feet and perioral area. The glucagon-induced hypoaminoacidaemia that develops in the majority of patients is implicated in the pathogenesis of the rash.

Glucose intolerance, with or without frank diabetes mellitus, develops in 85%, principally due to the hyperglycaemia that results from glucagon-stimulated hepatic glycogenolysis and gluconeogenesis. Weight loss is almost universal, and probably reflects the known catabolic actions of glucagon. Weight loss may be as severe as 20–30kg, and may occur even with small non-metastatic tumours. Normochromic, normocytic anaemia develops in 60% of patients, and is probably caused by an inhibitory effect of prolonged hyperglucagonaemia on erythropoiesis.[22] Other abnormal laboratory findings commonly found include hypoalbuminaemia (in 80% of patients), and hypocholesterolaemia (reduced VLDL in 80% of patients), which both reflect reduced hepatic synthesis.

Less common symptoms include; deep venous thrombosis (20%), pulmonary emboli (10%), diarrhoea (15%), and psychiatric disturbance.

Somatostatinoma

Somatostatinomas are usually solitary tumours, which originate in the pancreas or small intestine. They are rare tumours, and account for less than 5% of pancreatic neuroendocrine tumours. Somatostatinomas of the pancreas and small intestine differ in several respects: a clinical syndrome is encountered more frequently (18.5% versus 2.5%), the large size of the tumour (>20 mm)(85.5% versus 41.4%), the association with neurofibromatosis type 1 (von Recklinghausen's disease)(1.2% versus 43.2%), and the presence of psammoma bodies (2.5% versus 49.4%).[23] The majority of somatostatinomas are overtly malignant at presentation, and have evidence of metastatic spread to the liver and/or lymph nodes.[24]

Somatostatinomas release large amounts of somatostatin and cause a distinct clinical syndrome characterized by diabetes mellitus, gallbladder disease, and diarrhoea with steatorrhoea. Approximately 40% of patients with somatostatinomas remain asymptomatic, and the tumour is discovered incidentally. The development of diabetes mellitus, which is usually mild, is likely to be secondary to the inhibitory action of somatostatin on insulin, glucagon and growth hormone release, as well as the replacement of functional pancreatic tissue. Gallbladder disease may be a result of somatostatin inhibition of gallbladder emptying. Diarrhoea and steatorrhoea probably reflect inhibition by somatostatin of pancreatic secretion of enzymes and bicarbonate, gallbladder motility, and intestinal absorption of lipids.[17] All of these symptoms may also occur in patients treated with somatostatin analogues, such as octreotide. Other symptoms include weight loss, which may be secondary to malabsorption, and hypochlohydria, which is probably secondary to inhibition of gastric acid secretion.[17]

GRFomas

GRFomas are defined as extracranial tumours that are predominantly or exclusively composed of cells that synthesize and release growth hormone-releasing factor (GRF) (also known as GHRH), which leads to growth hormone (GH) hypersecretion and acromegaly. The average age of GRFoma patients at presentation is 40years, and at variance with pituitary adenoma, GRFoma is 3 times more common in women than in men. Differentiation of GRF-driven acromegaly from GH hypersecretion from a pituitary adenoma can be difficult. Radiological imaging of the sella turcica is often unhelpful, since 40–45% of patients with GRFomas show a hypophyseal mass resembling an adenoma, usually due to hyperplasia of somatotrophs. Detection of an extrahypophyseal tumour, together with an elevated plasma GRF level, is the most useful aid to diagnosis.

GRFomas have been reported in the pancreas (30% of cases), bronchus (50% of cases, where they can be associated with bronchial carcinoid tumours), and in the jejunum (15% of cases). Approximately 30% of tumours are overtly malignant at the time of diagnosis. About 40% of patients with GRFomas have other associated secretory syndromes, especially through the expression of the MEN-1 syndrome. Co-existing endocrinopathies include hyperparathyroidism, Zollinger-Ellsion syndrome, hypoglycaemia, Cushing's syndrome and phaeochromocytoma.[24]

ACTHomas

These tumours are very rare, and are usually located in the pancreas (90% of cases). They produce ACTH and ectopic Cushing's syndrome. The tumours often co-secrete, and so the syndrome is often associated with another syndrome. Approximately 95% have metastasised at the time of diagnosis.

NPTs Causing Carcinoid Syndrome

Tumours secreting 5-hydroxytryptamine (5HT) or pancreatic 'carcinoids' account for 1–2 % of NPTs. These tumours also produce other peptides such as histamine, kinins, substance P and prostaglandins. Unless these secretory peptides are released directly from metastases into the systemic circulation (intestinal drainage is into the portal system), they do not usually cause any signs or symptoms. Paracrine secretion in the intestine may however cause diarrhoea. Therefore, systemic features of the carcinoid syndrome only usually become apparent when liver metastases are present. This syndrome is characterised by flushing and diarrhoea, and less commonly by wheezing, abdominal pain and heart disease. Pancreatic carcinoids with excess production of histamine may cause an atypical carcinoid syndrome (generalised flushing, lacrimation, hypotension, cutaneous oedema, bronchoconstriction). Approximately 10% of carcinoid tumours are associated with MEN1.[25]

NPTs Causing Hypercalcaemia

Hypercalcaemia has been reported with NPTs secreting parathyroid hormone-related protein that mimics the actions of parathyroid hormone. The tumours are usually large and have metastased to the liver by the time of diagnosis.[17,26]

Nonfunctioning Tumours

The incidence of non-functioning pancreatic endocrine tumours is $1–2/10^6$ persons/year, and these tumours represent about 60% of the total number of pancreatic neuroendocrine tumours. By definition, nonfunctioning endocrine tumours of the pancreas are those that have all the histological characteristics of a pancreatic neuroendocrine tumour, but no associated clinical syndrome related to hormone hypersecretion. These tumours are often producing hormones, but remain clinically 'silent' for a number of reasons. The peptides or hormones produced may not produce a known specific clinical syndrome, for example, pancreatic polypeptide (PPomas), α- and β-human chorionic gonadotrophin, calcitonin, and chromogranin A. In other cases, the tumour may produce a peptide which is well known to produce a clinical syndrome, but fails to release it, or produces it at only very low plasma concentrations. It may also be that the tumour only produces biologically inactive precursor forms of the peptide, or that it simultaneously produces an inhibitory peptide, such as somatostatin.[27]

The tumours are usually unifocal, and are predominantly situated in the head of the pancreas. Between 20 and 40% of non-functioning pancreatic neuroendocrine tumours are MEN-1-associated, and in this situation may be multifocal. Patients present with symptoms related to expanding tumour mass, most commonly jaundice and epigastric pain, but also with weight loss, steatorrhoea, upper gastrointestinal bleeding, recurrent pancreatitis, fatigue and malaise. An increasing number are being detected incidentally. Reported malignancy rates at presentation are 60–90%.[29,30]

It should be noted that a tumour which has presented as a non-functioning tumour, can later turn into a functioning tumour, for example a gastrinoma.[27]

Diagnosis

Pancreatic neuroendocrine tumours produce specific symptoms and hormones. The diagnosis is therefore based on clinical symptoms, hormone measurement, radiological and nuclear medicine imaging and histological confirmation. The gold standard is histology and should be obtained wherever possible. The minimum diagnostic criteria for the various syndromes includes histology and the following tests:

Fasting Gut Hormones

Insulinoma

The demonstration of inappropriately high insulin levels in the presence of hypoglycaemia after prolonged fasting is used to diagnose insulin-producing tumours. Hypoglycaemia is usually defined as a blood glucose below 2.2 mmol/l (40 mg/dl). Within 24 h of fasting, most patients develop hypoglycaemia, and by 72 h, virtually all patients will be hypoglycaemic. Paired samples of insulin and glucose are taken every 3–4 h. The test is terminated, and intravenous glucose is administered, when the serum glucose drops to 2.2 mmol/l or below, and/or the patient becomes symptomatic. The test is considered positive for insulinoma if the ratio of plasma insulin (in μU/ml) to glucose (in mg/dl) is more than 0.3. A value of 20 pmol/mmol (insulin concentration [pmol/l] divided by glucose concentration [mmol/l]) can also be used to differentiate patients with and without insulinoma.[31]

Caution must be taken to exclude factitious hypoglycaemia, which may be particularly prevalent amongst medical workers or in relatives of diabetic patients. This can be done by measurement of C-peptide (endogenous flanking peptide of insulin) and pro-insulin (which is elevated in up to 90% of patients with insulinoma). Levels of these peptides will be normal or low following administration of insulin. In the case of deliberate or accidental use of sulphonyureas, elevated levels of insulin and C-peptide are found, but proinsulin levels are normal or low. In this case, serum can be screened for the presence of hypoglycaemics.[18]

Gastrinoma

The most important diagnostic test for gastrinoma is an elevated fasting serum gastrin in the presence of gastric acid secretion after discontinuation of acid reducing medications (ie. H2 receptor antagonists and proton pump inhibitors).

A level of greater than 1000 pmol/ml, is virtually diagnostic of ZES. However, hypergastrinaemia can also be present in a number of other conditions, including *Helicobacter pylori* infection, and gastric outlet obstruction. Many patients with ZES will have only a modest elevation of fasting serum gastrin (between 100 and 1000pmol/l), and in these patients a secretin stimulation test may be of some help.[25] Secretin is a potent stimulator of gastrin release from gastrinomas, but has little effect on other types of gastrinaemia.

Other Hormones

The diagnosis of glucagonoma syndrome can be made easily by measurement of fasting plasma glucagon. In the vast majority of patients with the syndrome, basal levels of glucagon exceed the normal range by six-fold.[21]

The Verner–Morrison syndrome can be diagnosed by demonstration of an elevated fasting plasma VIP level. The usual increase in plasma VIP is 50-fold above the normal mean concentration. A raised plasma pancreatic polypeptide level is frequently also seen in pancreatic VIPomas.[32]

Somatostatinoma

Plasma somatostatin levels are usually elevated in pancreatic somatostatinomas. Levels may however be inconclusive or normal in duodenal or small intestinal tumours.[17]

GRFoma

Plasma GRF (GHRH) levels are usually elevated in patients with GRFoma, and are normal in patients with pituitary acromegaly. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are invariably elevated, and GH levels fail to suppress after an oral glucose load in all forms of acromegaly.[33]

ACTHoma

These patients usually have an elevated plasma ACTH and high cortisol levels. This does not however differentiate an extra-pituitary ACTH-producing tumour from pituitary-dependent Cushing's disease, with which it may share some clinical features. Factors favouring the diagnosis of an extra-pituitary ACTH-secreting tumour include, the presence of hypokalaemia with metabolic acidosis, the co-secretion of other gut hormones, male sex, and advanced age.[34]

Chromogranin A

The chromogranins are a unique family of water-soluble acidic glycoproteins found in the storage vesicles of neuroendocrine cells and released during

exocytosis. Chromogranin A (CgA) was the first discovered chromogranin and is found throughout the diffuse neuro/endocrine system. It is an excellent immunohistochemical marker of neuroendocrine differentiation, and because it is co-released with resident peptide hormones/amines contained within the secretory granules, it can also serve as a serum marker of neuroendocrine activity. The serum concentration of CgA is elevated in patients with various neuroendocrine tumours. Nonfunctioning neuroendocrine tumours, for which no peptide marker is available, usually retain the ability to secrete CgA. CgA can therefore be used as a tumour marker for nonfunctioning neuroendocrine tumours. Elevated levels are strongly correlated with tumour volume.[35] CgA measurements are very reliable markers in the follow-up of treatment. Furthermore, increases in CgA usually precede radiological evidence of progression.[36] Independent observations that increased levels of chromogranin A correlate with a bad prognosis in different tumours might indicate that chromogranin A or its splice products act as stimulators of tumour growth. Other general markers for neuroendocrine tumours include pancreatic polypeptide and human chorionic gonadotrophin subunits.

Somatostatin and its analogues exert their effect via a family of G-protein-coupled receptors. So far, five subtypes have been cloned, somatostatin receptors 1–5 (sst1–5).[37] The natural compound, somatostatin 14, binds with high affinity to all the receptors. The only somatostatin analogues widely used clinically, octreotide and lanreotide, bind with high affinity to sst2 and sst5.[38] The somatostatin receptors have been identified on many normal cells of neuroendocrine origin, on inflammatory and immune cells, and on a large variety of human cancers. More than 90% of pancreatic endocrine tumours express two or more of the five subtypes of receptor at high density.[39, 40] Knowledge of this property of these tumours has been utilised in the development of *imaging techniques* and in novel therapeutic strategies. Radiolabelled somatostatin analogues, such as [Indium-111-diethylenetriamine pentaacetic acid (DTPA)-D-Phe^1]-octreotide (Ocreoscan), have proved to be very useful for tumour scintigraphy and internal radiotherapy of somatostatin receptor overexpressing tumours.

Assessment of Tumour – Localisation and Extent

The next key step in the management of pancreatic neuroendocrine tumours is the determination of the primary tumour location, and the tumour extent (location and extent of metastases). This information is essential both for patients whose disease is amenable to surgical resection, and for the clinical management of patients with advanced disease.

Somatostatin Receptor Scintigraphy (SRS)

Numerous studies have now established somatostatin receptor scintigraphy (SRS) using Indium-111-DTPA,D-Phe^1-octreotide as the initial imaging modality of choice in patients with any type of neuroendocrine tumour, except insulinoma. SRS has greater sensitivity in detecting both the primary tumour, hepatic metastases, and bone metastases,[41,42] than other conventional radiological techniques (computed tomography [CT], magnetic resonance imaging [MRI], ultrasound, and

angiography), and also allows the whole body to be scanned in one examination (Fig. 4.1). The sensitivity of detection of somatostatin receptor-positive tissues is further increased by performing single photon emission computed tomography (SPECT), which also gives a better anatomical delineation than planar views.[43,44]

Despite the high sensitivity of SRS, there are some limitations to its use. Since numerous normal tissues, as well as benign and pathological processes (for example, thyroid disease and breast disease), can have high densities of

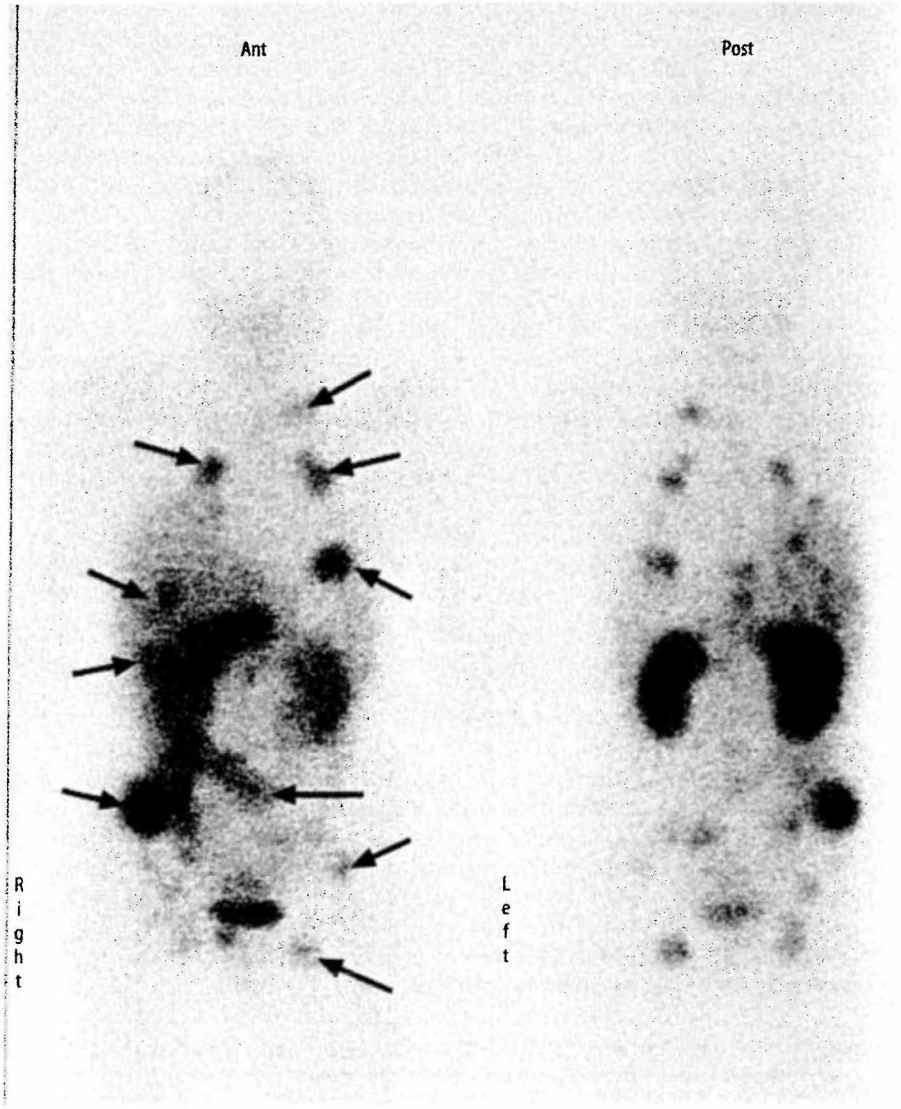

Figure 4.1. Indium-111-DTPA,D-Phe[1]–octreotide scan demonstrating avid uptake of tracer (indicated by the arrows) in a patients with multiple metastases from a PTHrP-secreting pancreatic neuroendocrine tumour.

somatostatin receptors, they can appear as focal lesions ('false-positive' localizations) in up to 15% of patients. The rate of 'false-positive' localisations can be reduced considerably if care is taken to consider the SRS with the clinical context.[45] Further, SRS detection rate is closely related to tumour size, and therefore may frequently miss small (ie. <1cm) gastroenteropancreatic tumours, most frequently at the primary site.[46] SRS fails to image insulinomas adequately for two reasons: the majority of these tumours are small (90% are <1cm in diameter), and only 50% of insulinomas express somatostatin type 2 receptors.[47] Finally, even with SPECT imaging, it may not be possible to adequately distinguish two or more closely-related images as being separate, which instead show as a single image. Given the above, SRS is not used alone, but in combination with CT and MRI in order to assess the localisation and extent of the tumour, in order to plan further treament, to monitor the effects of treatment, and to monitor the progression of disease.

Positron Emission Tomography

Positron emission tomography (PET) using the standard tracer ^{18}F-labelled deoxyglucose (FDG) is currently being assessed, but appears to have low sensitivity for well differentiated NPTs, but perhaps higher sensitivity for the more aggressive poorly differentiated tumours. The alternative tracers, ^{11}C-labeled 5-hydroxytrytophan and L-dihydroxyphenylalanine (L-DOPA) are also being assessed. ^{11}C-labeled 5-hydroxytrytophan has improved sensitivity in serotonin-producing (usually carcinoid) tumours. Currently, PET provides no advantage compared with CT and is ineffective in the detection of non-functional neuroendocrine pancreatic tumours.[48]

Control of Hormonal Symptoms

The third step in management of patients with pancreatic endocrine tumours is to control the symptoms of the hormone-excess state. Treatment with the somatostatin analogue octreotide has been shown to be clinically effective both in terms of improving the symptoms and reducing serum hormone levels in patients with VIPoma, glucagonoma, GRFoma, and 5HT-secreting pancreatic neuroendocrine tumours. Standard doses of octreotide (50–500μg 2–3 times a day subcutaneously) produce symptomatic and biochemical responses in 30–75% of patients over a mean duration of 12 months.[49] Both of these effects appear to be dose related. Since the response rate varies markedly between patients, it is important to titrate the dose of the octreotide until adequate symptom and biochemical control has been achieved.

Octreotide is well tolerated by the majority of patients. Adverse effects are generally mild and transient, lasting less than 1 week. They include diarrhoea, pain at the injection site, abdominal pain, nausea, and flatulence. Octreotide therapy is also associated with an increased risk of cholelithiasis in the long term. A significant recent advance is the development of long-acting forms of octreotide and sustained-release forms of lanreotide (Sandostatin LAR® and Somatuline® LA respectively). These depot forms are more convenient than the usual preparations of octreotide or lanreotide which usually need to be administered subcutaneously every 4 to 8 hours. Sandostatin LAR® is usually administered monthly; Somatuline® LA every 10 to 14 days.

Eventually, however, the majority of patients with neuroendocrine tumours show desensitisation to the effects of somatostatin analogues within weeks to months. The mechanism regarding this escape phenomenon is not yet clarified. Novel somatostatin receptor subtype-selective somatostatin analogues are being developed that may prevent desensitisation.[50]

The effect of long-acting somatostatin analogues in the prevention of hypoglycaemia in insulinoma patients is unpredictable. Hypoglycaemia may even be aggravated through the supression of counterregulatory hormones such as glucagon. Diazoxide inhibits the release of insulin from normal B cells and insulinoma cells, and may be effective in the prevention of hypoglycaemia patients with insulinoma. Long-acting somatostatin analogues can suppress gastric acid secretion, however its effects cannot compete with the acid-suppressing effects of agents, such as proton-pump inhibitors or histamine receptor antagonists, which should be given to Zollinger–Ellison patients.

Surgical Removal of Localised Disease/debulking

Surgery remains the only curative modality currently available for resectable neuroendocrine tumors. Complete surgical resection may be possible in those tumours that are localised at presentation (60% of gastrinomas, 90% of insulinomas, 10–20% of nonfunctioning tumours, and 10–40% of VIPomas and glucagonomas).[51] Furthermore, up to 15% of patients with a pancreatic neuroendocrine tumour and metastatic disease to the liver, have disease confined to one hepatic lobe, which may be resectable.[52]

The surgical management varies with tumour type, location and size. Benign insulinomas and gastrinomas less than 5cm in diameter may be treated with enucleation. Malignant gastrinomas more than 5cm in diameter should be managed with either a Whipple resection and periduodenal node resection or distal pancreatectomy, depending on the location of the tumour (most tumours are in the head of the pancreas). Intraoperative ultrasound should be performed during the surgical procedure. VIPomas, somatostatinomas, and nonfunctioning tumours should be treated with either excision or Whipple resection, with local lymph node resection. Most glucagonomas are malignant and located in the tail of the pancreas, therefore, distal pancreatectomy with resection of the peripancreatic lymph nodes and spleen is the recommended surgical treatment. Postoperative anticoagulation is also recommended because glucagonomas are associated with an increased risk of thromboembolic disease. Additionally, debulking of metastatic tumour can improve survival when cure cannot be achieved.

Prior to any surgery, or indeed any interventional treatment of neuroendocrine tumours, special care must be taken to assess the type of hormone production by the tumour, as large quantities of hormones may be released during the procedure. For glucagonoma, VIPoma, and 5HT-secreting pancreatic neuroendocrine tumours, preoperative treatment with octreotide is usually adequate. Patients with large insulinomas may require hypertonic glucose after tumour removal, and close glucose monitoring. Patients with gastrinoma should maintain their medication with proton pump inhibitors for a while after tumour resection, since they have elevated gastric acid secretion due to hypertrophic gastric mucosa[53]

The surgical treatment of pancreatic endocrine tumours in the setting of MEN-1 is slightly different. Tumours are frequently multiple, and patients with multiple tumours and MEN-1 may run a more indolent course.[54, 55] The surgical approach for MEN-1-associated gastrinomas remains controversial, because of their indolence, multiplicity, and reduced chance of achieving complete resection. There is no absolute clarity over whether intervention offers survival or disease-free benefit in these patients. Currently surgical intervention is advocated when the tumours exceed 2.5 cm in diameter, as tumour size is associated with a higher likelihood of liver metastases, which ultimately affects survival[56]

Antitumour Treatment in Patients with Advanced Disease

Metastatic neuroendocrine tumours of the pancreas progress at markedly different rates in individual patients. One recent study of patients with metastatic gastrinoma illustrates this observation.[57] In this series of patients who had not yet received antitumour treatment, 26% showed no tumour growth over a mean follow-up time of 29 months, 32% had slow growth (1–50% volume increase per month) over a 19-month period, and 42% had rapid growth (>50% volume increase per month) over an 11-month period. During a mean follow-up period of 3.1 years, 62% of the patients in the rapid-growth group died, but no patients in the no-growth or slow-growth growth group died. These results, and others, have led to the recommendation that patients with advanced tumour secondary to metastatic gastroenteropancreatic tumour should have their disease reassessed at an interval of 4–6 months after the initial staging investigations, and that only those patients with growing tumours should receive anti-tumour treatment at this stage.[52]

A number of different treatment modalities exist for patients with advanced metastatic disease. These will be discussed within two treatment categories: interventional management of liver metastases (below) and extrahepatic metastases (page 47).

Interventional Management of Liver Metastases

Liver Resection

Palliative liver resections can be considered for some patients with slow tumour growth and severe hormonal symptoms. There is a significant operative mortality for elective liver surgery and this must be taken into account. Prophylactic use of antibiotics has decreased infectious complications, but morbidity is still more frequently associated with sepsis than with bleeding during surgery.[50] Patients with bilobar or more than 75% liver parenchymal involvement are less likely to benefit from surgical resection.[58]

Hepatic Embolisation and Chemoembolisation

Hepatic artery embolisation provides an effective alternative treatment for hepatic metastases, with reduction in hormonal symptoms and pain[59] as well as

reduction in tumour burden (Fig. 4.1) and increase in median survival.[58] Immediately before embolisation an arteriogram is performed to demonstrate the arterial anatomy, tumour blood flow, and the patency of the portal vein. The hepatic arteries feeding the liver segment containing the metastases are then selectively embolised by filling the arterial tree distal to the point of injection with embolisation material, eg. polyvinyl alcohol (PVA) particles, causing a temporary, but complete ischaemia.[60] Objective response rates may be further improved by combining the embolisation material with cytotoxic agents. In a recent study using a combination of 5-fluorouracil and streptozotocin, a reduction in tumour size occurred in 50% of patients, and 90% of patients had improvement in symptoms due to hormone hypersecretion. The mean duration of the response was 24 months (range 6 to >63 months).[61] There are however no controlled trials to suggest that chemoembolisation is any better than particle embolisation alone. Again, this therapy should be used with caution when more than 75% of the liver parenchyma is replaced by tumour.[58] For large volume liver metastases, our practice is to perform particle embolisation of a single lobe, and if intra-arterial chemotherapy is to be given, that is injected into both lobes. The procedure is then repeated 2–3 months later with particle embolisation being performed on the other lobe.

Peroperative Techniques

Radiofrequency ablation (RFA), causing selective thermocoagulation, is a novel method for destroying liver tumours, and may be performed percutaneously or at laparotomy or laparoscopy. The latter approaches facilitate the use of intraoperative ultrasound scanning which may demonstrate occult hepatic disease and allow isolation of the liver from adjacent structures. Initial experience using laparoscopic RFA indicates that it is effective in reducing symptoms and achieving good local tumour control, and has low associated morbidity.[62] Other novel relatively non-invasive surgical techniques include *cryosurgery*[63] and the *interstitial laser* (γ-knife).

Taking advantage of the high expression of somatostatin receptors by pancreatic neuroendocrine tumours, intraoperative tumour detection techniques are evolving, using radiolabelled octreotide and a scintillation detector (*radioguided surgery*) to help localise mainly small tumours.[64]

Liver Transplantation

In patients with advanced metastatic disease which is confined to the liver, liver transplantation may be considered. The results from retrospective single and multicentric analyses show that most liver recipients experience significant liver palliation despite a high tumour recurrence rate, although in some patients a long-term cure can be achieved.[65] These series included gastroenteropancreatic tumours of various histological types, including carcinoid tumours. At a time of organ donor shortage, there is an ethical debate about transplanting tumour patients. Total hepatectomy and liver replacement should only be considered in patients with metastatic neuroendocrine tumours confined to the liver in situations where: the tumours are not accessible to curative surgery or major tumour

reduction, the tumours are causing symptoms that are not responding to medical or interventional treatment, or hormonal symptoms that are life threatening.[66] Rigorous pre-transplant work-up involving SRS with SPECT, and CT or MRI is required to exclude extra-hepatic disease.

Extrahepatic Metastases

Chemotherapy

Chemotherapy is generally only considered for advanced progressive pancreatic endocrine tumours (increase of >25% of the main tumour masses in a period of 12 months, or tumoural symptoms not treatable by other means).[67] A combination of streptozocin, 5FU and Adriamycin significantly prolongs survival, inhibits tumour progression, and produces major shrinkage of well-differentiated tumours in up to two-thirds of cases.[68] Its efficacy sometimes enables secondary surgical excisions, which were initially not possible, to be made. A similarly high response rate has also been reported using a combination of etoposide and cisplatin in undifferentiated endocrine tumours of the pancreas.[69] (Midgut and carcinoid tumours have a much lower response rate). Unfortunately, in all patients, there is a high rate of tumour recurrence or new progression at more than 12 months.

Biotherapy

Somatostatin. Recent studies have shown somatostatin analogues to have an anti-tumour-growth effect in a small proportion of patients with progressive malignant pancreatic endocrine tumours. The molecular mechanisms responsible for this effect are both direct and indirect. Direct action may result from blockade of mitogenic growth signal or induction of apoptosis following interaction with specific somatostatin receptors. Indirect effects include the reduced or inhibited secretion of bioactive peptides, that may have a growth-promoting effect on the tumour cells, inhibition of angiogenesis, and effects on the immune system.[70] Approximately 50% of patients demonstrated stabilisation of tumour progression when treated with standard or ultrahigh dose octreotide. Up to 6% of patients demonstrated a reduction in tumour size.[53,71]

Alpha-interferon. Alpha-interferon (α-IFN) is known to inhibit the cell cycle, to inhibit the production of growth factors and receptors secreted by the tumours, to have an-antiangiogenic effect, and an immuno-modulatory effect by stimulation of natural killer cells and macrophages. The biochemical response rate in pancreatic endocrine tumours treated with moderate doses of α-IFN (3–6 mega units given 3 to 7 times a week) is about 50%; tumour stabilisation occurs in approximately 80% of patients, significant tumour reduction occurs in only 15% over a mean duration of 20 months.[72] The use of polyethylene glycosylated recombinant interferons in the future will hopefully facilitate treatment and may reduce side-effects.

Combination of α-IFN and octreotide. In two recent studies on patients with progressive metastatic pancreatic endocrine tumours, the majority of patients,

who were not responding to either agent previously used alone, showed an improved response with the combination of α-IFN and octreotide.[73,74]

Receptor-targeted Therapy

The common expression of somatostatin receptors on pancreatic endocrine tumours and their avid uptake of Indium-111-DTPA,D-Phe^1-octreotide for scintigraphic scanning, has led to the development of receptor-targeted radionuclide therapy. The concept of targeted therapy is to visualise the tumour with the diagnostic scan and use this to make an estimate of tumour load. Then the isotope label on the peptide is changed, preferably for a β-emitter, in order to target the radiotherapy to the tumour cell ('magic bullet'). The path length of β-particles is several cells thick, and so the cross fire of the β-particles emitted from the radiolabelled peptide bound to the tumour cell can also, in theory, kill neighbouring somatostatin receptor-negative tumour cells. This assumption led to the development of Yttrium-90-DOTA-D-Phe^1-Tyr^3-Octreotide(^{90}Y-DOTATOC), a chelated somatostatin analogue with high affinity for the somatostatin receptor which is labeled with a β-emitting radionuclide. In a recent trial, predominately in patients with therapy resistant and progressive disease, therapy with this novel agent was well tolerated and had a remarkable objective response rate (36%), an improved survival rate (76% at 2 years), and a reduction in tumour-associated pain (12%).[75]

Yttrium-90-DOTA-lanreotide has also recently been developed, the design based principly on the high affinity of Indium-111-DOTA-lanreotide for sst 2,3,4, and 5, and relatively low affinity for sst 1. Preliminary treatment results from a multicentre trial in patients with progressive disease are promising, and again show that the treatment is well tolerated.[76] The results of a large Novartis sponsored trial with their Yttrium 90-DOTA analogue performed in patients with neuroendocrine tumours is awaited. Currently other radionuclide therapies using alternative isotopes are being assessed, including Lutetion-1777-DOTA-octreotide.

Indium-131-meta-iodobenzylguanidine(MIBG) therapy, based on a positive Indium-123-MIBG scan, produces symptomatic and hormonal improvement and modest tumour regression/stabilisation in patients with metastatic carcinoid tumours.[77] It has very much less effect on pancreatic endocrine tumours, probably reflecting the very much reduced sensitivity of Indium-123-MIBG in detecting these tumours (9% of tumours detected in one series).[78]

Bony Metastases

Painful bone metastases can be treated with either radiotherapy or in a clinical trial with bisphosphonates. Disseminated bony metastases may be treated with radionuclide therapy.

Prognosis

The prognosis of NPTs is still not entirely clear. The reasons for this are multifactorial. Part of the problem is that NPTs are relatively rare tumours, often with a slow

evolution, that are only diagnosed once they have widespread metastases. Another problem is that many studies have not differentiated between carcinoid tumours and NPTs, let alone between the different types of NPT. Gastrinomas are the most studied of the NPTs. Recent well-designed studies have yielded useful information about these tumours.[54,79] Firstly, that only 25% of patients with gastrinoma pursue an aggressive course, the rest pursuing a non-aggressive course. The 10-year survival was 96% in the indolent group, compared to a 10-year survival of 25% with the aggressive tumour course. The factors associated with a poor prognosis include: liver metastases (either initially or with the development of time); the extent of liver metastases; the development of bone metastases or ectopic Cushing's syndrome; a large primary tumour (>3 cm); female gender; MEN-1 absent; a short clinical course prior to diagnosis; a markedly increased gastrin prior to diagnosis; and a primary tumour that was pancreatic rather than duodenal. The development of bone metastases or ectopic Cushing's syndrome were particularly predictive of a poor prognosis, with patients only surviving 1.9 ± 0.4 and 1.7 ± 0.4 years after their diagnosis, respectively.[79]

There is much less data available on the other NPTs. The majority of insulinomas (>90%) are cured by surgical resection. The majority of patients with the remaining NPTs (particularly non-functional NPTs) have hepatic metastases at presentation. However numerous studies have shown that the presence of liver metastases, primary tumour size (>3cm) liver metastases progression, presence of other metastases, and the histological features of poor tumoral differentiation, are associated with a poor prognosis.

Developments in the Management of Neuroendocrine Pancreatic Tumours

NPTs are rare and complicated tumours, which often need complicated strategies for optimal management. The increasing number of investigative procedures and therapeutic options available to diagnose and treat NPTs requires the ability to coordinate specialists from a variety of disciplines including gastroenterologists, oncologists, interventional radiologists, nuclear medicine physicians, pathologists and surgeons. In order to do this, only a multidisciplinary approach in a specialist centre is appropriate. Furthermore, scientific research and controlled clinical trials are needed to determine the efficacy of the many treatment options available for these tumours. As they are rare, multicentre collaboration is very important and from this can be sought a consensus of opinion on guidelines for the management of carcinoid tumours based on the best evidence available. Organisations such as the European Neuroendocrine Tumour Group (ENET) and the UK Neuroendocrine Tumour Group (UK NETwork) and have been the first to take a lead in this multidisciplinary approach. We must also remember that patients with rare tumours need even more in the way of support, and hence the importance of developing readily available literature and patient support groups.

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