Pancreatic neuroendocrine tumours

What are pancreatic neuroendocrine tumours?

Pancreatic neuroendocrine tumours (PNETs) arise from amine precursor uptake and decarboxylation (APUD) stem cells, which are pluripotent neuroendocrine cells within the ductular epithelium of the exocrine pancreas and elsewhere in the distal foregut. Pancreatic endocrine tumours (PETs) are classified as neuroendocrine tumours.

Pancreatic neuroendocrine tumours are a diverse group of neoplasms with a generally favourable prognosis. Although they exhibit indolent growth, metastases are seen in roughly 60% of patients.[1]

PNETs can be divided into functional (exhibit a distinct clinical syndrome due to hormone hypersecretion) and non-functional tumours. The majority of PNETs are non-functional.[2] Non-functional tumours may secrete pancreatic polypeptide (PP), which appears to be a marker of PNETs but is not a mediator of any specific PP-related clinical syndrome.

PNETs are frequent and may be non-functional in patients with multiple endocrine neoplasia type 1 (MEN1).[3]

PNETs are classified as low-grade, intermediate-grade or high-grade tumours based on morphologic criteria and the proliferation rate.[4]

Liver metastases are the most common secondaries beyond spread to regional lymph nodes. Bone metastases may occur late in the course of the disease and indicate a poor prognosis. In rare cases, PNETs metastasise to the lungs or brain.

How common are pancreatic neuroendocrine tumours? (Epidemiology)

- Population-based studies have assessed the incidence of PNETs as 0.2-0.4 per 100,000.[5] However, there is a much higher prevalence of 0.5-1.5% in unselected autopsy specimens.
- PNETs account for about 3% of all primary pancreatic tumours.[6]
- Insulinomas and gastrinomas are equally common and account for more than half of all clinically apparent PNETs. Vasoactive intestinal polypeptide-secreting tumours (VIPomas) are one eighth and glucagonomas are one seventeenth as common. Somatostatinomas are even more rare.
- Most PNETs are sporadic but they occur in approximately 75% of cases of MEN1.
- PNETs occur in 40-80% of patients with MEN 1 syndrome and are mostly non-functioning tumours or gastrinomas.[7]
- PNETs appear to have a slightly higher incidence in women than in men. Patients with sporadic PETs present most often between 30-50 years of age. Patients with PNETs as part of MEN 1 syndrome tend to present between 10-30 years of age.
- PNETs can also arise within other syndromes, such as von Hippel-Lindau, neurofibromatosis type 1 and tuberous sclerosis complex.[8]

Symptoms of pancreatic neuroendocrine tumours (presentation)

- Functional tumours exhibit metabolic and clinical characteristics depending upon the pancreatic islet cell type they arise from:[5]

    - Insulinoma: confusion, sweating, dizziness, weakness, unconsciousness; fasting hypoglycaemia and relief of hypoglycaemic symptoms with eating or after glucose administration.
    - Gastrinoma: Zollinger-Ellison syndrome of severe peptic ulceration and diarrhoea, or diarrhoea alone.
    - Glucagonoma: necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea.
    - VIPoma: Verner-Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia, and achlorhydria (deficiency of hydrochloric acid in the stomach).
    - Somatostatinoma: cholelithiasis, weight loss, diarrhoea and steatorrhoea, diabetes mellitus.
    - Carcinoid tumours: 2-3% of carcinoid tumours are located in the pancreas.
    - Other rare clinical syndromes may occur - eg, calcitoninoma, parathyroid tumour, growth hormone-releasing factor-secreting tumour (GRFoma), adrenocorticotrophic hormone-secreting tumour (ACTHoma), neurotensinoma and serotonin (5-hydroxytryptamine)-secreting tumours (which are classified as carcinoid tumours).
    - Non-syndromic PNET: symptoms from pancreatic mass and/or liver metastases.

- Non-functional PNETs typically present later in the course of their disease, when their tumours begin to cause symptoms related to tumour bulk or symptoms derived from metastases. An abdominal mass may be felt if there is a large, non-functional tumour. Large, non-functional neoplasms in the head of the pancreas may occasionally cause jaundice as a result of biliary obstruction.

- Physical examination in patients with PNETs generally reveals nonspecific findings.
- Insulinomas are benign in approximately 90%; all other types of PET are malignant in over 50% of cases.[7]

Clinical examination to exclude complex cancer syndromes (eg, MEN1) should be performed in all cases of PNETs, and a family history taken.[5]

Insulinoma

- Episodic hypoglycaemia, usually in the early morning or after missing a meal, presenting with headache, light-headedness, confusion, visual disturbances, seizures, personality changes and even coma.
- Compensatory catecholamine excess can lead to palpitations, weakness, trembling, tachycardia and irritability.
- Insulinomas are the most common cause of hypoglycaemia resulting from hyperinsulinism but extrapancreatic insulin-producing tumours and self-induced hypoglycaemia due to the administration of insulin or sulfonylureas should be considered.

Gastrinoma

See separate Zollinger-Ellison Syndrome article.

- Abdominal pain and peptic ulceration of the upper gastrointestinal tract are the most common symptoms. The symptoms tend to be protracted and refractory to standard medical and surgical therapies.
- Symptoms of gastro-oesophageal reflux disease and dysphagia may occur.
- Diarrhoea occurs in more than a third of patients and steatorrhoea may also occur.

VIPoma

- The main symptom is severe watery diarrhoea causing weakness, hypotension, lethargy and weight loss. Abdominal cramps and nausea are common and flushing episodes may occur.
- Faecal potassium loss causes hypokalaemia.

Glucagonoma

- Dermatitis (necrolytic migratory erythema), nail dystrophy and stomatitis. Necrolytic migratory erythema is an erythematous rash, which typically begins in the groins and perineum and migrates to distal extremities, forming bullae which heal with hyperpigmentation. [9]
- Hyperglucagonaemia in patients with glucagonomas results in glucose intolerance (including diabetes) and weight loss (secondary to anorexia and increased catabolism).
- As many as a third of patients have secondary thromboembolic phenomena, with a history of deep venous thrombosis and/or pulmonary embolism.
- Normochromic normocytic anaemia may occur.

Somatostatinoma

- Somatostatinomas are associated with diabetes mellitus and anaemia.
- Postprandial fullness.
- Relative biliary stasis with gallbladder calculi and symptoms of biliary colic.
- Diarrhoea and/or steatorrhoea, with malabsorption and weight loss.
- May present late with hepatic metastases.

Investigations [5]

- Baseline blood tests should include plasma chromogranin A and urinary 5-hydroxyindoleacetic acid.

- Imaging:
    - For detecting the primary tumour, CT, MRI and somatostatin receptor scintigraphy (SSRS) are recommended.
    - Gallium-68 (^{68}Ga) positron emission tomography (PET)/CT is recommended for the detection of an unknown primary.
    - Additional imaging modalities may include endoscopic ultrasound (EUS), endoscopy, digital subtraction angiography (DSA) and venous sampling.
    - For assessing secondaries, ^{68}Ga PET/CT is the most sensitive modality. Where this is not available, SSRS in combination with CT is the most sensitive modality.
- Tumour biopsy is critical for PNET diagnosis, not only to demonstrate the neuroendocrine nature of the tumour but also to preliminarily grade the tumour and to perform immunocytochemical staining for hormones and islet markers, which is useful for determining the pancreatic origin of liver metastases.[10]

Diagnosis of clinical presentation

- Non-functioning pancreatic tumours:
    - It is recommended that serum chromogranin A and pancreatic polypeptide should be tested in patients with possible non-functioning pancreatic tumours.

- Insulinoma:
    - Fasting hypoglycaemia (<2.5 mmol/L) associated with an elevated insulin level (in the absence of exogenous administration of insulin).
    - Proinsulin and C-peptide test: proinsulin, C-peptide and insulin are all increased in patients with insulinoma. Administration of insulin causes elevated insulin levels but normal or low proinsulin and C-peptide levels.
    - Anti-insulin antibodies strongly suggest administration of insulin rather than insulinoma. Insulin antibodies, especially at high titres, may also indicate the presence of autoimmune hypoglycaemia.
- Gastrinoma:
    - Fasting serum gastrin levels.
    - Basal and maximal gastric acid secretion.
    - Secretin stimulation test: a large increase in the gastrin level of more than 200 ng/L above the basal level supports the diagnosis of gastrinoma.
- VIPoma:
    - Serum vasoactive intestinal polypeptide (VIP). Since VIP has a very short half life, the diagnosis is confirmed by the finding of elevated circulating histidine methionine, which is produced from the prepro-VIP molecule and co-secreted by VIPomas.
    - Pancreatic polypeptide levels are elevated in 75% of cases and neurotensin in 10%.
    - Low serum potassium and bicarbonate levels secondary to faecal loss. Hypomagnesaemia, hypercalcaemia and glucose intolerance are other common biochemical disturbances.
    - Low basal gastric acid output.

- Glucagonoma:
    - Serum glucagon levels greater than 1,000 ng/L are diagnostic of glucagonoma.
- Somatostatinoma:
    - Raised fasting serum somatostatin levels.
    - SSRS has been used to demonstrate hepatic involvement.

Localising the tumour

- High-resolution contrast-enhanced spiral CT scanning is the initial imaging technique used to localise and stage most PETs.
- MRI, SSRS or transduodenal endoscopic ultrasound may be useful for localisation of small tumours.[5]
- Provocative angiography can be used to map the location of occult gastrinomas and insulinomas.
- Selective transhepatic portal venous sampling: to help localise the tumour.
- Endoscopy: location and number of peptic ulcers. May reveal reflux oesophagitis.
- Intraoperative endoscopic transduodenal illumination may be helpful in the localisation of small PNETs located within the wall of the duodenum.
- Intraoperative ultrasonography is the study of choice for localisation of insulinomas and is more effective than any pre-operative diagnostic imaging study.

Treatment and management of pancreatic neuroendocrine tumours[5]

Surgical resection is still the only curative therapeutic option for localized pNETs. However, a debulking operation has also been proven to be effective for controlling the disease. As for drug therapy, steroids and somatostatin analogues are the first-line therapy for those with positive expression of somatostatin receptor, while everolimus and sunitinib represent important progress for the treatment of patients with advanced PNETs.

Surgery should be offered when PNETs are resectable or when debulking offers palliation. Surgery should be considered in those with liver metastases and potentially resectable disease.

Treatment choices for non-resectable disease include somatostatin analogues, biotherapy, targeted radionuclide therapy, locoregional treatments (eg, ablation or chemoembolisation) and chemotherapy. External beam radiotherapy may relieve bone pain from metastases. Chemotherapy may be used for inoperable or metastatic pancreatic PNETs. Chemotherapy may be used for poorly differentiated PNETs. Sunitinib or everolimus may be used for patients with advanced (inoperable or metastatic), progressive, well-differentiated PNETs.

Ablation: for patients with metastatic PNET, ablation is most often used for small-volume tumours or in combination with resection. Ablation and resection have been shown to be useful for symptom relief. Image-guided ablation can contribute to cytoreduction of metastatic disease.

Initial management

Many PNET syndromes are potentially life-threatening at presentation. Initial treatments for specific syndromes may include:

- Insulinoma: may initially require immediate potassium replacement and dextrose administration. Hypoglycaemia can often be managed in the pre-operative period by administering diazoxide.
- Gastrinoma: treatment is directed at stabilising the general haemodynamic condition of the patient, controlling bleeding from gastrointestinal ulcers and establishing a non-acidic gastric pH with the use of proton pump inhibitors.

- VIPoma-associated diarrhoea: replacement of volume losses and the correction of acid-base and electrolyte abnormalities.
- Glucagonomas: often require blood transfusions, total parenteral nutrition and pre-operative control of hyperglycaemia.
- Somatostatinoma syndrome: nutritional support and control of hyperglycaemia are important aspects of care.

Subsequent management

- Somatostatin analogues:
    - The only effective medication for functional pancreatic endocrine neoplasms is a long-acting somatostatin analogue (eg, octreotide), which is effective for all functional PNETs except somatostatinoma.
    - Octreotide is also a useful adjunct in palliative treatment of patients with most functional metastatic PNETs.
    - Patients with VIPoma frequently respond dramatically to small doses of somatostatin analogues with cessation of diarrhoea.[5]
    - Somatostatin analogues are not useful in the treatment of patients with somatostatinoma syndrome.
- Interferon alfa:
    - Interferon alfa-2a and alfa-2b: patients with PETs have shown good response with human leukocyte interferon.
    - The combination of alfa-interferon and somatostatin analogues has been shown to be beneficial for the treatment of patients with advanced malignant PNETs.

- Insulinoma:

    - Diazoxide can be used to reduce insulin secretion for patients with insulinomas. When used with hydrochlorothiazide, its hyperglycaemic effect is increased.
    - Patients with unresectable insulinoma may gain benefit by eating frequent small meals with a high starch and complex carbohydrate content.
    - Exercise often exacerbates the symptoms of insulinoma syndrome secondary to relative substrate deficiency such as hypoglycaemia. Therefore, patients with insulinoma may need to avoid exercise until their tumour is successfully resected.

Chemotherapy

Primarily reserved for patients with PNETs that are metastatic and/or unresectable. No benefit from chemotherapy has been demonstrated in patients with metastases to only lymph nodes.

Surgery

Surgery is the primary treatment for localised tumours and five-year survival rates are 80-100% in resectable cases.[11] Radical surgery has a central role in the therapy of PETs. Increasing numbers of PNET resections are now being performed by laparoscopic pancreatic surgery.[12]

Surgical management of the primary tumour is similar for the different types of pancreatic endocrine neoplasms. Surgical treatments may include:

- Small benign lesions remote from the main pancreatic gland: resection of the tumour.
- Tumours deep in the substance of the pancreatic gland and tumours larger than 2 cm in diameter: regional pancreatectomy. Lesions in the head or uncinate process of the pancreas can be resected with pancreaticoduodenectomy. Permanent diabetes mellitus can occur following extensive pancreatic tumour resection.

- When a pre-operatively occult gastrinoma is not found during surgical exploration, despite the use of intraoperative ultrasonography and endoscopic transduodenal illumination, longitudinal duodenotomy can be performed to assess for duodenal microgastrinomas. The localised microgastrinomas can be resected and the duodenal defect closed.
- Selective provocative angiography should be performed for an occult insulinoma or gastrinoma so that the appropriate pancreatic segment can be resected.
- Metastatic disease to the liver should be resected when possible. Aggressive surgical therapy in patients with advanced disease may prolong survival.[2] Surgical resection or hepatic arterial embolisation of hepatic metastases, with or without chemotherapy, are effective. In patients with unresectable disease, radiofrequency or cryosurgical ablation should be considered.
- Liver transplant or splenectomy may be required for metastatic disease.

Prognosis

The prognosis is very variable, depending particularly on the type and stage of the PNET.[13]

However, prognosis is generally favourable and is significantly better than for pancreatic exocrine cancer.[14]

Further reading

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14. General Information About Pancreatic Neuroendocrine Tumors (Islet Cell Tumors); US National Cancer Institute

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