Islet cell tumours: diagnosis and medical management

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Islet cell tumours are difficult to diagnose. They are rare tumours that secrete hormones resulting in symptoms and signs that are often mistaken for more common conditions. Benign and solitary tumours are surgically resected, while medical therapy aims at symptom control and palliation of malignant disease.

Islet cell tumours are often slow growing and their clinical manifestations are usually the result of excess peptide hormone secretion. In malignant disease, palliation is often possible through suppression of peptide release or blocking of the action of the peptide hormone. Non-functioning tumours have a worse prognosis and present with local pressure symptoms or symptoms such as anorexia and weight loss. Although functioning tumours produce and secrete a single major peptide, these tumours frequently produce other gastrointestinal peptides. The clinical picture may therefore change with time and with treatment.

Islet cell tumours may also secrete parathyroid hormone-related peptide (PTH-rp) resulting in hypercalcaemia, growth hormone-releasing hormone (GHRH) resulting in acromegaly and corticotrophin releasing factor/adrenocorticotrophin (CRF/ACTH) resulting in Cushing's syndrome. Islet cell tumours may be associated with the autosomal dominant syndrome of multiple endocrine neoplasia type 1 (MEN-1) with features of parathyroid disease, pituitary and pancreatic tumours. This review describes the various islet cell tumours, their diagnosis and medical management (Taheri et al, 2000).

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INSULINOMA

Insulinoma has an annual incidence of 0.5–1 per million. Over 80% of tumours are benign solitary adenomas, often less than 1 cm in diameter. Approximately 8% of insulinomas are associated with MEN-1. Insulinomas can occur at any age, but the majority occur in middle age with a female preponderance. When associated with MEN-1, insulinomas occur at an earlier age, are often multiple, and in up to 25% of cases are malignant (Grant et al, 1996).

Hypoglycaemia results in symptoms of neuroglycopenia (Dizon et al, 1999) and symptoms resulting from the catecholaminergic response. Patients with neuroglycopenia may complain of headache, lethargy, dizziness, diplopia, blurred vision and amnesia. Rarely, hypoglycaemia results in seizures, coma or permanent neurological deficit. The catecholaminergic response is associated with tremor, anxiety, palpitations, nausea, hunger and sweating. Hypoglycaemic episodes occur early in the morning and may be triggered by exercise. To prevent symptoms, patients often increase their carbohydrate intake, which usually results in weight gain. The causes of hypoglycaemia are listed in *Table 1* (Service, 1995).

The diagnosis of insulinoma depends on the demonstration of Whipple's triad (Whipple and Franz, 1935): symptoms of hypoglycaemia, biochemical evidence of hypoglycaemia (plasma glucose <2.2 mmol/litre), and relief of symptoms with sugar intake. In insulinoma, hypoglycaemia is associated with inappropriately elevated plasma insulin (>30 pmol/litre) and plasma C-peptide (>300 pmol/litre), in the absence of sulphonylureas in the plasma and urine. Exogenously administered insulin is associated with raised plasma insulin, but low plasma C-peptide levels. The 72-hour fast is the gold standard test in insulinoma (*Table 2*). In most series, 30% of patients develop symptoms at 12 hours into the fast, 80% within 24 hours and 100% at 72 hours (Grant, 1996).

Since surgical resection is curative in most patients, preoperative localization of the tumour is carried out. Computed tomography (CT) scanning can detect 20–40% of insulinomas and is most useful for staging and management of malignant insulinoma. Transabdominal ultrasound has comparable detection rates to CT.

Selective arterial stimulation with calcium in conjunction with hepatic venous sampling has been successfully used for tumour localization.

Medical therapy is for patients awaiting surgery, for failed surgery, for inoperable metastatic disease, or for poor operative risk patients. Frequent meals or snacks are often effective in symptom control. Guar gum can reduce insulin secretin in insulinoma. Diazoxide (200–600 mg/day orally) suppresses insulin secretion but side-effects, such as fluid retention, hirsuitism and weight gain, occur in 10–50% of patients. Serious adverse effects include cardiomyopathy, bone marrow suppression and cardiac arrhythmias. Cytotoxic chemotherapy for malignant insulinoma includes the combination of streptozotocin and 5-fluorouracil, or streptozotocin with doxorubicin. The latter combination has been reported to result in 69% tumour regression rate with a median duration for remission of 18 months (Moertel et al, 1992). The embolization of hepatic metastases may also provide relief.

TABLE 1.
Causes of hypoglycaemia

Insulin or insulin-like mediated	Insulinoma
	Non-β-cell islet tumours
	Exogenous insulin administration
	Insulin autoantibodies
	Retropertitoneal sarcomas
	Nesidioblastosis (β-cell hyperplasia)
Drugs	Sulphonylureas (especially longer acting drugs and in the elderly), ethanol, quinine, haloperidol, salicylates
Enzyme deficiencies	Glycogen storage disease
Hormone deficiencies	Cortisol (Addison's disease)
	Growth hormone (pituitary failure)
	Glucagon
	Catecholamine, e.g. postoperative resection of phaeochromocytoma
Critical organ failure	Liver disease, renal failure, heart failure, starvation, sepsis, shock
Other	Intense exercise
	Ackee fruit

TABLE 2.
Diagnostic tests for insulinoma

The 72-hour fast. Gold standard diagnostic test	Patient is admitted to hospital for close supervision
	Intravenous cannula is positioned and patency confirmed
	Only non-caloric drinks and water are permitted; activity is encouraged
	Plasma glucose is measured at regular intervals dictated by glucose values
	If the patient becomes symptomatic — blood is taken for plasma glucose, insulin and C-peptide, and blood and urine for sulphonylurea screening
	If plasma glucose is < 2.2 mmol/litre, the test is terminated and the above additional blood samples sent to the laboratory
	The patient can then be fed
C-peptide suppression test. For diagnosis of recurrent insulinoma and in patients who have a borderline positive 72-hour fast	Intravenous cannula is positioned
	Exogenous insulin (0.1 U/kg) is infused over 60 minutes
	In insulinoma, insulin infusion fails to suppress C-peptide levels
Provocation tests	Tolbutamide, glucagon, intravenous or oral glucose tolerance test — these are generally unnecessary

GASTRINOMA (ZOLLINGER–ELLISON SYNDROME)

Gastrin-producing tumours (Zollinger and Ellison, 1955) have an annual incidence of one per million. The mean age at the onset of symptoms is 50 years with a male preponderance. Up to a third of gastrinomas are associated with MEN-1 while up to a half of MEN-1 patients develop gastrinomas. The majority of gastrinomas arise in the gastrinoma triangle, an area containing the duodenum, pancreatic head and the hepatoduodenal ligament. At presentation, up to 50% of patients with gastrinoma have metastases, mainly to the liver.

The diagnosis of gastrinoma is considered in patients with unusual or complicated peptic ulcer disease that is refractory to treatment that includes *Helicobacter pylori* eradication (Jensen, 1996). Oesophagitis and diarrhoea are common. The increased acid secretion secondary to elevated gastrin levels neutralizes digestive enzymes and damages the intestinal mucosa, resulting in diarrhoea. Diarrhoea that persists in spite of fasting and that is relieved by acid antisecretory drugs is suggestive of a gastrinoma.

Gastrinoma is diagnosed by high levels of fasting serum gastrin in the face of high basal gastric acid secretion (>15 mmol/hour). Several conditions can result in raised gastrin levels (*Table 3*). Histamine H_2-blockers and proton pump inhibitors (PPIs) should be discontinued for at least 72 hours and at least 14 days respectively before fasting gastrin is measured. Since hypercalcaemia raises gastrin levels, hyperparathyroidism should be excluded in patients with MEN-1. The secretin provocation test is carried out when gastrin levels are borderline and acid secretion results equivocal (Jensen, 1996). Up to 87% of patients will demonstrate a positive response to secretin (gastrin levels paradoxically increase by at least 50% from baseline).

Tumour localization is carried out to identify the small proportion of patients (9%) with local-

ized disease who may benefit from curative surgery. Radiolabelled octreotide scanning usefully detects the primary tumour and any metastases. Magnetic resonance imaging (MRI) provides information regarding hepatic metastases. Small tumours may be detected with endoscopic ultrasound and/or selective arterial angiography in combination with CT scanning. Intra-arterial secretin injection at the time of angiography may aid localization. Surgical exploration, in conjunction with intraoperative ultrasound, duodenal transillumination and duodenotomy, may be necessary to localize any solitary tumour not detected by the above techniques.

Symptomatic control can be achieved with PPIs at dosages titrated to the patient's response and aimed at reducing gastric acid secretion to <10 mmol/hour for the hour before the next dose of the drug. Somatostatin analogues (*Figure 1*) and gastric surgery may be necessary in a few patients. Solitary tumours are surgically excised in an attempt to cure the patient. With metastatic disease, symptoms are controlled well with PPIs for many years. When symptoms become difficult to control or the tumour behaves more malignantly, then somatostatin analogues, debulking surgery, chemotherapy, α-interferon therapy, hepatic tumour embolization, and treatment with radiolabelled somatostatin analogues are available options.

In malignant gastrinoma, combination chemotherapy with streptozotocin and chlorozotocin or doxorubicin results in tumour regression with a median duration of up to 18 months. The majority of patients benefit from hepatic tumour embolization through reduction of local pressure symptoms. α-interferon therapy results in tumour regression in some patients, but is not well tolerated. Liver transplantation in association with removal of the primary tumour has been attempted, but at present is not used routinely. The 5-year survival of patients with liver metastases is 20% compared to 81% in those without metastases. The management of non-metastatic gastrinoma in MEN-1 patients has been difficult because of lack of information regarding the natural history of gastrinoma in these patients.

VIPOMA (VERNER–MORRISON SYNDROME)

VIPomas (Verner and Morrison, 1958; Bloom et al, 1973), tumours secreting vasoactive intestinal peptide (VIP), have an annual incidence of 1 per 10 million. The mean age at presentation is 49 years with a slight female preponderance. Ninety per cent of VIPomas are pancreatic. VIPomas are usually solitary (1–7 cm diameter) with 37–68% having metastasized at the time of diagnosis, usually to the liver and regional lymph nodes. Extrapancreatic VIPomas occur along the autonomic nervous system, in the retroperitoneum, lungs, jejunum, liver, and in the adrenal.

TABLE 3.
Causes of hypergastrinaemia

Associated with low gastric acid/achlorhydria	Atrophic gastritis — pernicious anaemia
	Acid antisecretory drugs — proton pump inhibitors, histamine H2-blockers
	Chronic renal failure
	Helicobacter pylori infection
	Post acid-reducing surgery
Associated with high gastric acid	*Helicobacter pylori* infection
	Gastric outlet obstruction
	Antral G cell hyperplasia
	Retained gastric antrum post-surgery
	Intestinal resection and short bowel syndrome
	Gastrinoma (Zollinger–Ellison syndrome)

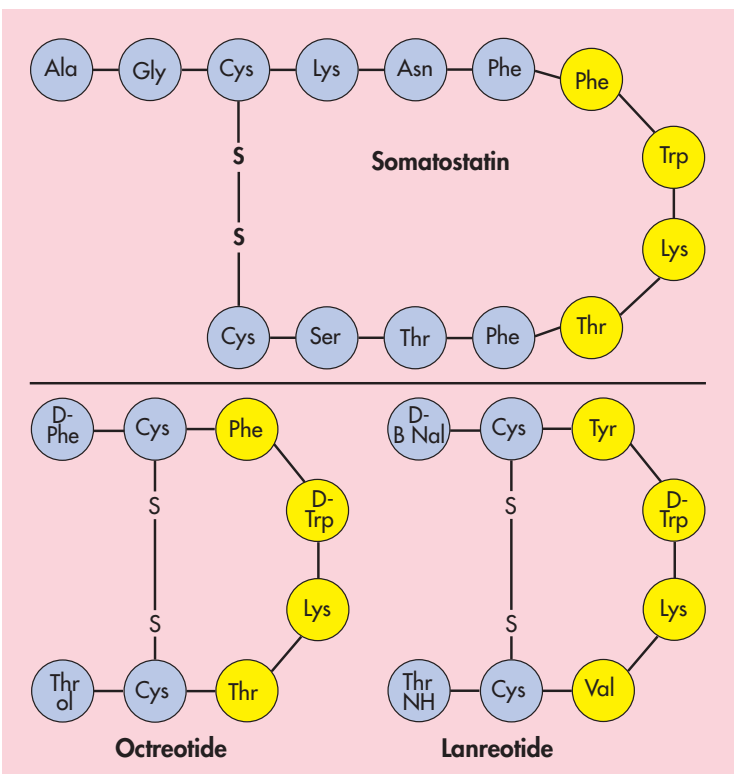

Figure 1. The structure of somatostatin-14 and the somatostatin analogues octreotide and lanreotide. The amino acids responsible for somatostatin receptor binding are in yellow. Octreotide is short acting and is usually given subcutaneously three times a day. Longer acting intramuscular somatostatin analogues (octreotide long-acting release and lanreotide long-acting release) are likely to be used increasingly. Side-effects of these drugs include pain at injection site, diarrhoea, steatorrhoea, flatulence, gallstones, hyperglycaemia, alopecia and water intoxication.

Elevated circulating VIP results in secretory diarrhoea (initially intermittent, but later continuous) with fluid, chloride, bicarbonate, potassium and magnesium loss from the small intestine. Hypochlorhydria occurs in 73% of cases. Stool volumes can reach up to 20 litres/day, despite fasting, and potassium losses can be greater than 400 mmol/day. The stool is otherwise normal. The severe hypokalaemia is frequently accompanied by metabolic acidosis as a result of bicarbonate loss in the stool. The average duration of symptoms before diagnosis is about 3 years. Other features of the syndrome are hypercalcaemia, glucose intolerance and mild diabetes mellitus. In up to 20% of patients, flushing of the head and trunk may occur in association with a patchy erythematous rash.

The diagnosis of VIPoma requires the demonstration of secretory diarrhoea associated with elevated plasma VIP levels (usually greater than 200 pg/ml). The plasma levels of peptide-histidine-methionine (a peptide product of the same precursor as VIP), pancreatic polypeptide and neurotensin may also be elevated. VIPomas, being large, can be localized by ultrasound, CT and radiolabelled somatostatin receptor scintigraphy. Up to 87% of VIPomas express somatostatin receptors. Rare small tumours may require more invasive localization techniques.

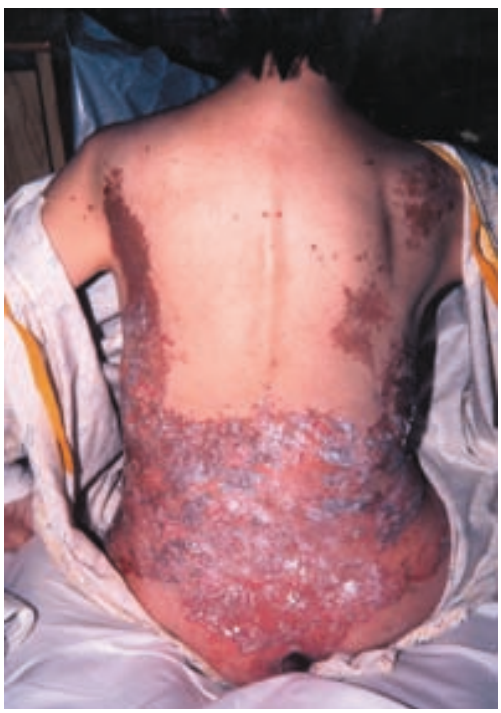

Figure 2. Necrolytic migratory rash of glucagonoma. The rash usually starts in the groin and perineum and then gradually migrates to the distal extremities. The initial lesions are erythematous macules, which become raised and bullous. The lesions then break down and heal, often leaving a residual area of hyperpigmentation. The rash is intensely painful and pruritic and secondary infections are common.

Treatment of VIPoma requires measures to restore fluid, electrolyte and acid-base balance. Specific treatment involves somatostatin analogues, which inhibit VIP secretion. Longer acting somatostatin analogues and longer lasting preparations of octreotide are likely to be used increasingly (*Figure 1*; Culler, 1999). Second line agents include glucocorticoids, indomethacin, lithium carbonate, and phenothiazines. Surgical tumour debulking can be beneficial in symptom control. VIPomas are sensitive to chemotherapy with good response to combination therapy with streptozotocin and 5-fluorouracil.

GLUCAGONOMA

Glucagonomas secrete glucagon and other preproglucagon-derived peptides (Bloom and Polak, 1987). These tumours have an annual incidence of 1 per 20 million. The median age at presentation is 62 years with a slight female preponderance. Twenty per cent of glucagonomas occur in association with MEN-1. The non-specific nature of the symptoms can delay the diagnosis for up to 10 years and may account for the fact that over 70% of the patients have metastatic disease at presentation.

The most characteristic feature of glucagonoma is the presence of a necrolytic migratory erythematous rash (*Figure 2*). The underlying cause of the rash is unknown but several factors such as direct action of glucagon on the skin, amino acid and fatty acid deficiency, and zinc deficiency have been implicated in its aetiology. Mucosal involvement results in stomatitis, cheilitis and glossitis. Cachexia is also a common feature of glucagonoma and is difficult to treat. Other manifestations include impaired glucose tolerance, normocytic anaemia, nail dystrophy, diarrhoea, tendency to venous thrombosis and pulmonary embolism, and neuropsychiatric symptoms.

Glucagonoma is biochemically diagnosed by highly elevated fasting plasma glucagon levels. Plasma glucagon may be elevated in other conditions, but these are easily distinguishable from glucagonoma (*Table 4*). Elevated plasma gastrin, insulin, pancreatic polypeptide, VIP and urinary 5-hydroxyindoleacetic acid (5-HIAA, a serotonin metabolite) levels have all been observed with glucagonoma.

The majority of glucagonomas are large and metastatic at presentation. Tumour localization can be achieved with ultrasonography, CT or visceral angiography. Somatostatin receptor scintig-

raphy is most useful for determining the extent of metastatic disease. Endoscopic ultrasound is sensitive for the detection of pancreatic primaries. Localized solitary tumours may require multiple techniques for localization.

Localized, solitary glucagonomas should be surgically excised. The glucagonoma rash responds to oral and topical zinc, and somatostatin analogues. Unfortunately, with time, the tumour may become less responsive to somatostatin analogues requiring increasing doses and/or measures to reduce tumour bulk. Warfarin anticoagulation is used for thrombotic episodes. Psychiatric symptoms, such as psychosis or depression, require appropriate assessment and treatment. Palliative measures for metastatic glucagonoma include surgical debulking, hepatic tumour embolization and chemotherapy.

SOMATOSTATINOMA

Somatostatinomas have an annual incidence of 1 per 40 million. They mostly occur in the pancreas, but can also arise in the duodenum. Pancreatic tumours present late with hepatic metastases and a syndrome characterized by the triad of cholelithiasis, diabetes and steatorrhoea. Other features include anaemia, hypochlorhydria, post-prandial fullness, hypoglycaemia (occasionally), and weight loss. Highly elevated plasma somatostatin levels confirm the diagnosis. Tumour localization uses the same techniques as described for the other tumours. Treatment is mainly surgical and the palliative measures are similar to those used for other tumours.

CONCLUSIONS

Islet cell tumours are rare tumours that secrete hormones resulting in a number of syndromes. PPIs can now protect patients with gastrinoma against complications of hyperacidity. Developments in the delivery of somatostatin analogues are likely to improve the quality of life for patients with islet cell tumours. The treatment modalities available for palliation of malignant disease vary between centres and depend on local expertise. The importance of novel treatments such as radiolabelled somatostatin analogues in tumours expressing somatostatin receptors remains to be determined. HM

TABLE 4.
Causes of raised plasma glucagon levels

Prolonged fasting	
Organ failure	Liver
	Kidney
Drugs	Oral contraceptive pill
	Danazol
Injury	Trauma
	Burns
	Sepsis
Endocrine	Diabetic ketoacidosis
	Cushing's syndrome

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KEY POINTS

- Islet cell tumours are rare tumours associated with excessive secretion of peptide hormones. These tumours may be associated with the syndrome of multiple endocrine neoplasia type-1.
- Most insulinomas, presenting with symptoms of hypoglycaemia, are benign adenomas while other islet cell tumours have greater malignant tendency.
- With the availability of proton pump inhibitors, gastrinomas now rarely present with complicated peptic ulcer disease, but may present with slow healing peptic ulcers, with oesophagitis and/or with diarrhoea.
- The most characteristic feature of the glucagonoma syndrome is the necrolytic migratory rash that can easily be mistaken for more common rashes such as psoriasis.
- Patients with VIPoma may present with diarrhoea, which may result in severe fluid, electrolyte and acid–base disturbances.
- The diagnosis of islet cell tumours requires high clinical alertness followed by appropriate endocrine and imaging investigations.
- Proton pump inhibitors have had a great impact in the treatment of gastrinoma in preventing complications of hyperacidity.
- Recently, new longer-lasting preparations of somatostatin analogues have become available and are likely to be used increasingly in the treatment of islet cell tumours.