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REVIEW

Islet cell tumours

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Abstract

Islet cells tumours are a range of rare neoplasms of neuroendocrine origin arising in or close to the pancreas. The normal islet cells of Langerhans in the pancreas contain B-cells (which secrete insulin), A-cells (which secrete glucagon), D-cells (which secrete somatostatin), D1-cells (which secrete pancreatic polypeptide) and D2-cells (which secrete vasoactive intestinal peptide). The majority (85%) of islet cell tumours secrete one or more of these hormones, or other substances not normally found in the adult pancreas (although often present in the foetal pancreas), notably gastrin.

Keywords: *Islet cell tumours; insulinomas; gastrinomas; glucagonomas; VIPomas; somatostatinomas; pancreatic polypeptide.*

Functioning tumours

Functioning tumours are named according to the main hormone produced and usually present with the clinical features of this excessive hormone secretion. These tumours may be either benign or malignant, solitary or multiple, or form part of the multiple endocrine neoplasia (MEN) syndrome. The diagnosis is almost always made biochemically and the role of imaging is to localise the tumour prior to surgery and to look for evidence of malignancy.

Insulinomas

Insulinomas are the most frequent functioning pancreatic tumours accounting for 60% of all islet cell tumours[1]. They cause spontaneous hypoglycaemia, relieved by glucose, and are associated with high levels of plasma insulin and C peptide levels. Insulinomas are malignant in 10%, multiple in 10% and 4% are associated with MEN type I. The tumours are usually very small: 90% are less than 2 cm and 50% less than 1.3 cm in diameter[2]. When multiple, the individual lesions are usually even smaller (mean diameter 9 vs. 13 mm)[3]. Patients with MEN type I usually have multiple small tumours. Malignant insulinomas tend to be larger than benign ones (2.5–12 cm in diameter)[2].

Gastrinomas

Gastrinomas are the second most common functioning islet cell tumours of the pancreas accounting for 18% of all islet cell tumours[1]. They give rise to the Zollinger–Ellison syndrome, which comprises increased gastric acid secretion, diarrhoea and peptic ulceration. The diagnosis is established by the demonstration of a raised fasting serum gastrin level with high basal gastric acid output. Over 90% of gastrinomas are found in the 'gastrinoma triangle' bounded by the third part of the duodenum, the neck of the pancreas and the porta hepatis[4]. Gastrinomas are multiple in 20–40% of patients and often extra-pancreatic, with 20% found in the duodenum. Gastrinomas are frequently malignant with metastatic spread occurring to the liver and local lymph nodes. They tend to be small: 38% of pancreatic and all duodenal tumours are less than 1 cm in diameter at diagnosis. One-third of cases are associated with MEN type I in which multiplicity is the rule and there is a tendency to recurrence.

Glucagonomas

Glucagonomas cause non-ketogenic diabetes mellitus and a characteristic migrating, necrolytic rash, as well

as stomatitis, diarrhoea and venous thrombosis. The tumours have an average diameter of 4–7 cm at diagnosis and are malignant in approximately 60% of cases.

VIPomas

VIPomas produce watery diarrhoea, hypokalaemia and achlorhydria (Verner–Morrison syndrome). The tumours range in diameter from 2 to 7 cm at diagnosis. The site of the tumour is intrapancreatic in 90% of cases, with the remainder (mainly gangliomas or ganglioneuroblastomas) originating in the sympathetic chain or adrenal medulla. Most extrapancreatic tumours are benign, but 50% of pancreatic VIPomas are malignant.

Somatostatinomas

Somatostatinomas are very rare, slow-growing tumours, which produce the clinical triad of gallstones, diabetes mellitus and steatorrhoea. These tumours arise from the pancreas in 50% and the duodenum in 50% of cases. Duodenal somatostatinomas occur in association with neurofibromatosis and are usually periampullary in position.

Pancreatic polypeptide

Pancreatic polypeptide is often secreted in association with other hormones. Isolated secretion is very rare and does not produce a recognised clinical syndrome.

Non-functioning tumours

Non-functioning tumours account for 15% of pancreatic neuroendocrine tumours[1]. They do not usually present until the tumour is large enough to cause symptoms from mass effect. The tumours tend to be large, solid and malignant, but are usually slow growing.

Imaging islet cell tumours

Transabdominal ultrasound

Transabdominal ultrasound is generally the first-line investigation. On ultrasound (US), islet cell tumours are usually seen as a well-circumscribed mass of lower echogenicity and finer echotexture than the normal pancreatic parenchyma. There may be a hyperechoic rim and larger tumours may show evidence of necrosis or calcification. A few lesions, especially gastrinomas, may be hyperechoic. Some lesions are isoechoic and are seen due to a hypoechoic halo around the lesion or due to the distortion of the gland. In malignant tumours, liver metastases are mostly hyperechoic or heterogeneous[2]. Larger lesions may show evidence of cystic degeneration. The overall detection rate for insulinomas is about 25–63%, but is up to 70% if the pancreas is adequately visualised. The reported detection rate for gastrinomas is lower with only 30% identified[5]. The sensitivity is better for intrapancreatic gastrinomas than extrapancreatic lesions. The relatively low sensitivity of transabdominal US is mainly due to overlying bowel gas.

Endoscopic ultrasound (EUS)

Endoscopic ultrasound (EUS) allows high-frequency probes (7.5–12 MHz) to be placed in close proximity to the pancreas and duodenum. In experienced hands, it has proved sensitive in detecting tumours of the pancreatic head but has been less successful for lesions of the pancreatic tail and duodenum. It is also possible to detect gastrinoma located in the bowel wall. Sensitivities as high as 79–100% have been reported[6–9]. EUS is superior to transabdominal US[10]. The procedure is expensive and invasive and the equipment and expertise are not widely available. Its eventual role remains to be defined.

Intraoperative ultrasound

Intraoperative ultrasound provides high-resolution images with 7.5–10 MHz probes. Like EUS, it is highly operator-dependent, but in experienced hands it is extremely effective for the identification of insulinomas at surgery. It is much less effective, however, for the identification of gastrinomas, since it is unable to identify extrapancreatic tumours of this type[11,12]. Intraoperative US does not replace preoperative localisation of islet cell tumour in most institutions but is used as an adjunct to palpation.

Computed tomography (CT)

Computed tomography (CT) is the most widely used method for localising islet cell tumours. Most islet cell tumours are isodense on unenhanced CT and will not be seen without intravenous (IV) administration of contrast medium unless they are large enough to deform the pancreatic outline. Occasionally small tumours may be apparent as a hypodense mass. Calcification may occur in up to 20% of cases and is more common in malignant than benign tumours[13–15]. Larger lesions may show central necrosis and are also more likely to calcify. On contrast-enhanced CT, islet cell tumours are generally seen as a rounded area that enhances more than the surrounding pancreas, although hypodense lesions do occur[16].

With spiral CT it is now possible to perform two-phase data acquisition of the pancreas in both the arterial and parenchymal phases following IV contrast

enhancement[17]. This has improved the sensitivity of CT for the detection of small islet cell tumours[17,18]. Primary islet cell tumour and metastases are usually better seen on the arterial phase than the delayed phase[19]. The reported sensitivity of CT in detecting primary islet cell tumours is 44–80% depending on the size of the tumour[2].

Hepatic metastases are generally highly vascular and are seen as low attenuation areas on unenhanced CT. Central necrosis is common in larger lesions and calcification may occur. Following IV contrast the lesions are enhanced. A solitary lesion may be indistinguishable from a haemangioma.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is increasingly being used in the localisation of islet cell tumours. The advent of fast spin-echo, fat saturation and dynamic contrast-enhanced imaging has resulted in greatly improved imaging for pancreatic lesions[20]. Studies comparing MRI and CT have shown that MRI has greater sensitivity than CT, particularly for smaller islet cell tumours[21]. In general, islet cell tumours are of lower signal intensity on T1-weighted images and of higher signal intensity on T2-weighted images than normal pancreas[22,23]. As on CT, the lesions tend to be enhanced following IV administration of contrast agent such as gadolinium[21].

Arteriography

Arteriography remains an important tool in localising neuroendocrine tumours. As with other imaging investigations, attention to the details of the technique is required for the best results. Unless superselective studies are performed the tumour may be missed[24] so selective arteriography of the superior mesenteric artery, the splenic artery, the gastroduodenal artery, the dorsal pancreatic artery, common hepatic artery and any accessory hepatic arteries should be included. Hepatic arteriography is performed both to demonstrate the arterial anatomy for the surgeon and to identify any liver metastases.

Islet cell tumours typically appear as a well-circumscribed blush in the capillary and early venous phase. Abnormal feeding vessels may be seen in large tumours. Angiographic features of malignant lesions include tumour irregularity, marked tortuosity of the feeding vessels, arterial encasement and venous obstruction[25].

The reported sensitivity of selective angiography for insulinoma is between 54 and 89% and for gastrinomas between 64 and 100%[2]. In patients with multiple tumours the sensitivity for individual lesions is lower. Lesions may be missed on angiography because they are too small or hypovascular or are obscured by the blush of adjacent bowel or spleen. False-positives result from misinterpretation of blush of adjacent bowel, splenunculus, or angiomas.

Venous sampling

Venous sampling allows functional radiological localisation of insulinomas and gastrinomas.

Transhepatic portal venous sampling (TPVS)

Transhepatic portal venous sampling (TPVS) is performed by transhepatic catheterisation of the right portal vein with a 5F catheter. Samples for hormonal analysis are obtained from the splenic vein, superior and inferior mesenteric veins, and portal and pancreatic veins. The exact location of the tumour cannot be pinpointed in the same way as in an imaging study and TPVS only localises the tumour to a region of the pancreas. Problems of interpretation may also arise when there are multiple tumours or if the hormone gradient is low. Transhepatic portal catheterisation is an invasive procedure with a significant complication rate and mortality[26].

Arterial stimulation and venous sampling (ASVS)

Arterial stimulation and venous sampling (ASVS) involves selective pancreatic arterial injections of a secretagogue (calcium for insulinoma and secretin for gastrinoma) and hepatic venous outflow is sampled. When arteries supplying the tumour are injected there is a rise in the hepatic venous hormone concentration. Lesions not seen on cross-sectional studies can be detected[27].

The sensitivity of ASVS is comparable to portal venous sampling for localisation of insulinoma and better than portal venous sampling for localisation of gastrinomas[28,29]. It can be performed as part of pancreatic angiography and involves none of the risks associated with portal venous sampling, such as hepatic arteriovenous fistulae, haemobilia and superior mesenteric vein occlusion. Despite these possible complications, portal venous sampling may occasionally be useful in patients with suspected insulinomas if all other preoperative studies are negative; properly performed, it is the most sensitive preoperative test for localisation of insulinomas, with a sensitivity of 80–90%[30].

Scintigraphy

For neuroendocrine tumours of the pancreas and bowel scintigraphy can be performed using radiolabelled somatostatin analogues and vasoactive intestinal peptide ([^{123}I]VIP). Table 1 summarises the proportions of tumours that are scan-positive. The radiolabelled somatostatin analogue, [^{111}In]pentetreotide, is able to image a variety of somatostatin receptor-positive tumours. The main advantages of scintigraphy are its ability to image

the whole body and to detect tumours or their metastases as small as 1 cm in diameter, especially in areas not under clinical suspicion. These imaging techniques can also be used to monitor the effects of therapy[31]. These small tumours can also be located at surgery using hand-held gamma probes.

Table 1 Proportions of tumours that are scan-positive

Type of tumour	[^{111}In]Pentetreotide (%)	[^{123}I]VIP (%)
Gastrinomas	80	—
Glucagonomas	95	—
Carcinoid	86	85
Insulinomas	61	82
Somatostatinomas	100	—
VIPomas	80	100

Localisation of islet cell tumours

The localisation of islet cell tumours presents a challenge to the radiologist as several imaging techniques are capable of demonstrating the tumour and no one technique is superior to the others.

A rational approach to the localisation of these tumours requires careful consideration of cost, sensitivities and availability of the imaging techniques. In most cases, initial imaging with a combination of US and CT or MRI will demonstrate the tumour and hepatic metastases. If these tests are negative or equivocal, arteriography (with ASVS) is the next line of investigation. If the tumour remains undetected, further investigation depends on local expertise. EUS is emerging as a highly sensitive test for small pancreatic tumours and may also demonstrate extrapancreatic gastrinomas. Intraoperative US is a useful adjunct to palpation at the time of surgery. Somatostatin receptor imaging is useful in somatostatin receptor-positive tumours not detected by other imaging techniques.

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