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EDITORIAL

Occult sporadic insulinoma: Localization and surgical strategy

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Abstract

Insulinomas continue to pose a diagnostic challenge to physicians, surgeons and radiologists alike. Most are intrapancreatic, benign and solitary. Biochemical diagnosis is obtained and imaging techniques to localize lesions continue to evolve. Surgical resection is the treatment of choice. Despite all efforts, an occult insulinoma (occult insulinoma refers to a biochemically proven tumor with indeterminate anatomical site before operation) may still be encountered. New localization preoperative techniques decreases occult cases and the knowledge of the site of the mass before surgery allows to determine whether enucleation of the tumor or pancreatic resection is likely to be required and whether the tumor is amenable to removal *via* a laparoscopic approach. In absence of preoperative localization and intraoperative detection of an insulinoma, blind pancreatic resection is not recommended.

Key words: Insulinoma; Occult; CT scan; Endoscopic ultrasonography; Surgery; Laparoscopy

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INTRODUCTION

Although rare, insulinomas are the most common functioning islet cell tumor of the pancreas. Recognition of the key neuroglycopenic symptoms should trigger the initial investigation. Biochemical proof of endogenous hyperinsulinemic hypoglycemia establishes the diagnosis. Several options are available for imaging and localizing these tumors. The tumors are usually small, single, benign, well-circumscribed, and evenly distributed throughout the pancreas. This tumor may be a part of the multiple endocrine neoplasia type 1 (MEN-1) syndrome. Surgical treatment is the only curative method. Patients are almost invariably cured lifelong with complete excision of a benign insulinoma[1-10]. Medical therapy can control hypoglycemic symptoms in approximately 50%-60% of patients with insulinoma, but operation remains the only curative treatment. The urgency of surgery is related to the severity of symptoms and the ability to manage them medically. In general, if hypoglycemia can be managed medically, there is less immediate pressure on the surgeon to find and remove the tumor. However, if symptoms are poorly controlled with medical management, the operation must be successful[5].

Most of the time it is easy to diagnose, localize and remove insulinoma, allowing complete alleviation of the dramatic, and sometimes life-threatening, symptoms of neuroglycopenia. Sometimes, however, this may not be so; despite adequate knowledge of its size and location, an insulinoma may be "occult" (occult insulinoma refers to a biochemically proven tumor with indeterminate anatomical site before operation) and difficult to localize[11-14]. What is (are) the technique(s) of choice to localize insulinoma? What surgical approach will be adopted in case of occult insulinoma? To respond to this important issue, we must discuss the different localization studies with operative procedure options.

EPIDEMIOLOGY OF INSULINOMA

Insulinoma are rare and small neuroendocrine tumors with an incidence of approximately one to four per million per year. It is the most common pancreatic islet cell tumor (25% of endocrine pancreatic tumors) and is malignant in only 5%-11% of cases. Virtually all insulinomas are intrapancreatic in location[1,3,5]. Extrapancreatic insulinomas with symptoms of hypoglycaemia are extremely rare (2%) and are most commonly found in the duodenal wall. In its sporadic form (90%) tumors are generally solitary, whereas in its familial form (5%-10%), they are multiple, especially in the setting of the multiple endocrine neoplasia (MEN) type 1 syndrome. Approximately 80%-90% of insulinomas are less than 2 cm in size and the lesions are distributed equally throughout the head, body and tail of

the pancreas. Most insulinomas are benign (90% of cases). Two per cent of patients have diffuse islet cell hyperplasia, microadenomatosis, or adult nesidiblastosis. Although insulinoma may occur throughout life, the mean age at presentation is 45 (range 8-82) years, and there is a female preponderance (female to male ratio 1.4:1). In MEN 1 the mean age at presentation is younger, at 25 years or less[1-5].

CLINICAL PRESENTATION

Almost all patients with an insulinoma present with symptoms of hypoglycemia secondary to excessive and uncontrolled secretion of insulin[11]. In the case of an insulinoma, symptoms are typically evident in the morning after an overnight fast, and are often precipitated by exercise[15]. Patients learned to avoid symptoms by eating frequent small meals and sugary snacks, with resultant weight gain. Symptoms are often misinterpreted, non-specific, episodic, vary among individuals and can differ from time to time in the same individual. So it is important to obtain a plasma glucose level during symptoms because a normal value in this case rules out the possibility of an insulinoma[5]. Hypoglycemic symptoms can be divided into two categories: neuroglycopenic and neurogenic symptoms[16,17]. Neuroglycopenic symptoms are due to central nervous system neuronal glucose deprivation. They include behavioral changes, confusion, lethargy, weakness, transient motor deficits, difficulty awakening, visual changes, fatigue, seizures and loss of consciousness[18-20]. If hypoglycemia is severe and prolonged, death may result. Neurogenic symptoms are are due to autonomic nervous system discharge caused by hypoglycemia. This results in cholinergic symptoms including hunger, sweating and parasthesia, and adrenergic symptoms including anxiety, tremor and palpitations. Erroneous psychiatric or neurological diagnoses are common in such situations and, on average, it takes up to 2 years before the correct diagnosis is made[5].

CLINICAL EVALUATION

In general, venous plasma glucose levels higher than 3.9 mmol/L after an overnight fast are normal; levels between 2.8 mmol/L and 3.9 mmol/L suggest hypoglycemia and lower than 2.8 mmol/L indicates hypoglycemia. Accurate diagnosis relies upon demonstration of symptomatic hypoglycemia with objective biochemical evidence of cell hypersecretion in the absence of factitious use of an insulin secretagogue. Whipple originally proposed the diagnostic triad of symptomatic hypoglcemia induced by fasting, a blood glucose level below 2.48 mmol/L (0.45 g/L), and prompt relief of symptoms following administration of glucose[5]. A corresponding rise in C-peptide is crucial to verify that insulin secretion is endogenous and to exclude factitia, i.e. self administration of insulin or peroral antidiabetic medication, claimed to be more common than insulinoma. Undetectable C-peptide in a hypoglycemic patient with an elevated insulin level would indicate exogenous insulin administration. Proinsulin levels in normal individuals are usually < 20% of total immunoreactive insulin but tend to be higher in patients with insulinoma. Proinsulin/insulin ratio > 50% may indicate malignant insulinoma, but occurs also with 25% of benign insulinomas. Oral sulphonylurea antidiabetics may cause hypoglycaemia with rise in insulin, C-peptide and proinsulin, and should be excluded by plasma measurement. The use of a ratio of insulin to glucose to aid in the diagnosis has been advocated by some authors but have evidence that they may be misleading. In one series, 34% of patients with excised insulinomas had insulin to glucose ratio > 0.30, demonstrating the fallibility of this ratio. The absolute values of glucose and insulin are the keys: when the glucose level drops to 0.45 g/L, any measurable insulin is abnormal[5,21-23]. A supervised 72 h fast forms the basis for the diagnosis of endogenous hyperinsulinemia[24,25]. The critical pathophysiological feature is failure of insulin secretion to fall to very low rates during episodes of hypoglycemia. From published reports, symptoms develop in 35% of patients within 12 h, 75% within 24 h, 92% within 48 h and 99% within 72 h[22]. The presence of hypoglycemic symptoms with fulfillment of the following criteria is diagnostic of insulinoma: blood glucose level 2.5 mmol/L or lower, insulin level 6 units/mL or higher, C-peptide level 0.2 nmol/L or higher, plasma proinsulin level 0.5 nmol/L or higher, plasma beta-hydroxybutyrate 2.7 mmol/L or lower, change in blood glucose of 0.25 g/L or higher at 30 min after 1 mg intravenous glucagon, and a negative sulphonylurea screen in the plasma and/or urine[21].

DIFFERENTIAL DIAGNOSIS

Hypoglycemia due to excessive endogenous insulin secretion can be caused by a primary pancreatic beta cell disorder including an insulinoma, beta cell hyperplasia or nesidioblastosis (presence of diffuse microadenomatosis, in which multiple small non-encapsulated tumors or nodules are distributed throughout the pancreas), a beta cell secretagogue including a sulphonylurea or a beta cell-stimulating antibody, or an antibody to insulin[20,26-29]. The differential diagnosis of hypoglycaemia includes hormonal deficiencies, hepatic insufficiency, exogenous hyperinsulinism, medication, drugs and enzyme defects. Occasionally differentiating insulinoma from these other causes of hypoglycaemia can be quite difficult. Hypoglycemia was reported in the setting of some tumors and of advanced gastrointestinal stromal tumors. Patients with multiple myeloma or systemic lupus erythematosus (SLE) and hypoglycaemia may have anti-insulin antibodies. These antibodies bind and release insulin in an unregulated manner, resulting in hypoglycaemia. These patients can be distinguished from patients with insulinoma by an anti-insulin antibody test[20,30-32].

LOCALIZATION STUDIES

The localization of small functioning islet cell tumors has proved a challenge to endocrinologists, surgeons and radiologists for several decades. No single imaging test has

emerged as being clearly superior. Imaging to localize insulinomas should only take place once the diagnosis has been confirmed biochemically. The role of imaging is not to diagnose insulinomas, but to identify and localize the tumor. Because virtually all insulinomas are found in the pancreas, it should be the focus of attention; no ectopic insulinomas have been encountered throughout the Mayo Clinic experience[3]. A number of techniques are available to localize an insulinoma, including transabdominal ultrasonography, abdominal computed tomography (CT), magnetic resonance imaging (MRI), arteriography, endoscopic ultrasonography (EUS), transhepatic portal venous sampling, selective arterial calcium stimulation with heptic venous sampling, 111 In-labelled octreotide scan with single photon emission tomography, intraoperative ultrasonography and intraoperative palpation.

Conventional preoperative techniques

Conventional imaging studies such as ultrasonography, computed tomography, and magnetic resonance imaging fail to reveal the majority of insulinomas[5,33-36]. The reported sensitivity of conventional CT scan, MRI, and ultrasonography for detection of pancreatic insulinoma ranges from about 30% to 66%, 37% to 71%, and 9.6% to 61% respectively. Combined Conventional CT scan, MRI and ultrasonography identify 17% to 66% of insulinoma[5,36-39]. With these conventional preoperative techniques, occult insulinoma was present in 31% to 52% of cases in some series[12,13]. The incidence of patients with occult insulinomas seen at the national institutes of health, increased from 16% to 52%[13].

Arteriography was considered the 'gold standard' for insulinoma localization. However, reported sensitivities of 29%-64%, combined with improved non invasive imaging modalities, have decreased its use[33-35,40,41].

Intraoperative techniques

Because of the inability of conventional preoperative studies to localize an insulinoma accurately, some have recommended surgical exploration with intraoperative ultrasonography (IOUS), thereby avoiding other costly preoperative imaging techniques. The most effective method for localizing an insulinoma at surgery is intraoperative ultrasonography[42-48]. Combining many of the attributes of preoperative ultrasonography but also enhanced by the ability to image the pancreas directly without the interference of overlying organs or gas, IOUS has been highly useful in localizing these small tumors. However, it is labour intensive, extremely operator dependent, and, without any definite preoperative localization, obviously focuses the immediate pressure to localize the tumor on the shoulders of the radiologist and ultimately the surgeon. Relevant operative anatomy can be examined to determine the optimal resection method with respect to proximity of the tumor to the main pancreatic duct, combined with colour flow Doppler assessment of adjacent major vessels. It can guide the safest approach to a tumor and facilitate dissection from the pancreatic duct, and also reveal tumor bilobation that has to be appreciated at enucleation. Sensitivities of up to 95% are reported in the detection of pancreatic insulinomas especially useful for tumors in the thicker pancreatic head. Islet cell tumors appear as well-defined, hypoechoic lesions on ultrasonography. The insulinoma is seen as a sonolucent and discrete mass. IOUS is now considered a necessary prerequisite for insulinoma operation together with complete pancreatic exploration and palpation at surgery. The IOUS should be done by an experienced investigator, and can identify tumors larger than 2-3 mm.

Most insulinomas are intraoperatively palpable as a firmer nodule with sensitivity of 90%. Tumors deep within the pancreatic head and in the uncinate process are difficult to palpate, and any lesion is difficult to detect in patients with previous pancreatitis. Combination of IOUS and palpation increases the sensitivity of insulinoma detection to nearly 100%, but requires complete surgical exploration. The head of the pancreas is delivered by the Kocher manoeuvre, with the uncinate process carefully dissected towards the porto-mesenteric vein. The pancreatic tail is mobilized to the mesenteric vein, allowing bidigital palpation and IOUS investigation from both dorsal and ventral surfaces[43,45,48].

Intraoperative laparoscopic ultrasonography greatly facilitates tumor localization and is valuable in guiding the site of pancreatic transection or enucleation especially with respect to the pancreatic ducts. It also defines the relationship of the tumor to the mesenteric vessels and confirms the adequacy of resection. Additionally, it readily demonstrates the relevant operative anatomy, defining the relationship of the tumor to the pancreatic and bile duct, and adjacent blood vessels[49-52].

New preoperative techniques

Transabdominal ultrasonography with frequency probes of 7.5-12 MHz allows higher image resolution. The advent of helical CT scanning has improved the detection of insulinomas compared with conventional CT[5,53-56]. Much investigation has gone into determining the optimal phase for detection and the consensus shows that the use of CT in the early phases is the most sensitive. Diagnostic sensitivity was 94% for dual-phase thin-section multidetector CT, 56% for dual-phase multidetector CT without thin sections and 29% for sequential CT. MR imaging is usually reserved for the detection of small and non-organ-deforming pancreatic tumors, including the functional islet-cell tumors. In current practice MRI is a second-line investigation, but potentially could take over from CT in the future as it becomes more widely available and expertise improves. For some authors, magnetic resonance imaging enables localization of small pancreatic insulinomas[57-62]. For others, while tumor detection increases with tumor size, MRI has been shown to be more accurate than CT, especially for the detection of smaller tumors. Multiple lesions are more difficult to detect using either modality. Current studies still emphasize that MRI is more sensitive for tumor detection. Nevertheless, in many institutions worldwide, CT remains the main imaging method for assessment of pancreatic disease, due largely

to its wide availability.

EUS appears to be emerging as one of the best preoperative studies to identify insulinoma. However, it requires considerable specialized expertise, is observer dependant and is not available in all centers. Sensitivities of up to 94% (range 57%-94%) are reported[63-65]. It has a specificity of 95% for identifying intrapancreatic insulinomas. The combination of biphasic thin-section helical CT and EUS resulted in an overall diagnostic sensitivity of 100%[66]. The EUS appearances of insulinoma are characteristic and include homogenous hypoechoic, rounded lesions with distinct margins. The availability of linear and curvilinear array EUS has broadened its applicability, with the ability to perform fine-needle aspiration cytology of suspicious lesions, contrast-enhanced EUS using Levovist and preoperative marking of lesions to facilitate surgical excision[67-72]. EUS can reveal important relation to the pancreatic duct, and if introduced in the horizontal duodenum allows visualization also of the uncinate process; some of the equipment may be used for tumor biopsy. It has appeared as the most efficient method for preoperative localization, although some isoechoic (6%) or pedunculated tumors may fail to be visualized. Other limitations of EUS include poor evaluation of lesions in the distal body or pancreatic tail[73,74]. Detection rates of 83%-100% of head and body lesions are reported compared with 37%-60% for pancreatic tails lesions[5]. Intraduct ultrasonography has been used to identify small islet cell tumors, and shows promise in differentiating benign from malignant causes of localized stenosis of the main pancreatic duct. It has a reported detection rate of over 90% in the diagnosis of 1-3-mm diameter lesions. However, it is not widely available, requires specialist skills to perform and interpret, and will probably remain confined to selected centres[75,76].

Transhepatic portal venous sampling and selective arterial calcium stimulation with hepatic venous sampling have been proposed as the most sensitive preoperative localization techniques by some authors[77-84]. Selective arterial calcium stimulation with hepatic venous sampling is a more sensitive and specific provocative test, and has largely replaced transhepatic portal venous sampling. This technique has a reported sensitivity of over 90% (range 87.5%-100%) in the accurate localization of pancreatic insulinomas. Although selective arterial calcium stimulation with hepatic venous sampling has a high detection rate, it is not used routinely in most centers as it is invasive, technically demanding and expensive. It may be appropriate when an insulinoma is strongly suspected but all non-invasive imaging tests are negative.

Insulinomas have a low density of somatostatin receptor in only 50% of tumors[85]. Consequently, somatostatin receptor scintigraphy has a limited role in the evaluation of primary insulinomas. Evolving techniques include peptide receptor scintigraphy combined with anatomic imaging methods such as CT or positron emission tomography[57,65]. In tumors that express somatostatin receptor, this can be determined along with detailed axial imaging. This technique has a role in tumor localization, and also for follow-up after treatment with peptide receptor radionuclide therapy[86-93].

PREOPERATIVE LOCALIZATION IS NECESSARY?

Avoiding all efforts at preoperative localization has been espoused by some because a relatively high percentage of insulinomas can be identified intraoperatively in the hands of experienced surgeons. However, reports of insulinomas that remain undetected range from 10% to 27% in several series and preoperative localization was considered essential to successful surgical treatment' in 15 of 41 (37%) patients at one major medical centre with a highly experienced endocrine surgeon. There is absolutely no question that positive localization is required prior to reoperative insulinomas. Preoperative localization is very helpful in planning the operation and certainly offers a measure of comfort to both the surgeon and patient prior to entering the operating room. However, preoperative imaging enables more accurate surgery, which may spare the patient an unnecessary total pancreatectomy and its associated morbidities, and facilitates the detection of metastases. Furthermore, it avoids prolonging the duration of surgery and potential intra-operative damage to major structures such as the splenic vein. It is agreed by the majority, however, that knowledge of the site of the tumor before surgery is helpful in that it allows one to determine not only whether enucleation of the neoplasm or pancreatic resection is likely to be required but also whether the tumor is amenable to removal *via* a laparoscopic approach. It should also mean that the operation itself can be performed more rapidly, thereby reducing its reported morbidity and mortality. Many surgeons emphasize the importance of preoperative localization of insulinomas, because 10%-20% of these lesions cannot be identified during surgical exploration. With recent advances in non-invasive imaging giving a detection rate fast approaching that of intra-operative imaging, the present consensus is generally that preoperative localization is worthwhile. The combination of biphasic thin-section helical CT and EUS resulted in an overall diagnostic sensitivity of 100%[66] and constituted the preoperative localization study of choice.

OPERATIVE MANAGEMENT

Surgical resection is the treatment of choice and offers the only chance of cure. Overall cure rates of 75%-98% are reported after surgery, with prognosis dependant on the stage at presentation and whether complete resection was achieved[94-98]. The surgery may use laparoscopic or open techniques, and includes enucleation, and/or resection. With advances in laparoscopic techniques, both laparoscopic enucleation and resection of pancreatic insulinoma have been performed successfully in many centers, and can be associated with markedly reduced hospital stay and increased patient comfort[99-124]. The operation is facilitated by laparoscopic ultrasonography, but may be complicated-especially in the case of pancreatic head tumors-by higher risk of pancreatic effusion (20%-40%). This operation can be chosen for carefully

selected lesions and should be performed by expert laparoscopists. Enucleation is indicated for small, benign tumors at least 2-3 mm from the main pancreatic duct. Intraoperative ultrasonography can be used to measure the distance between the tumor margin and the main pancreatic duct. Macroscopically, lesions appear reddish-brown in colour in contrast to the surrounding yellowish pancreatic parenchyma, and possess a pseudocapsule with a clear plane of dissection between the tumor and the surrounding soft pancreatic parenchyma. Recent guidelines suggest enucleation is enough if the lesion is clearly localized before surgery, near or at the pancreatic surface, and easily defined intraoperatively. Histologic confirmation of complete excision and the benign nature of the insulinoma are essential[66]. Resection is indicated when the tumor abuts the pancreatic duct or major vessels, or where malignancy is suspected with a hard, infiltrating tumor and puckering of the surrounding soft tissue, distal dilatation of the pancreatic duct or lymph node involvement[102]. Resection options include distal pancreatectomy (with or without splenectomy), pylorous-preserving Whipple procedure, or mid-body pancreatectomy, depending on the site of insulinoma. To determine completeness of tumor excision, a perioperative insulin assay is valuable[125-127]. Intraoperative frozen section can provide information regarding the nature of the tissue, but is often non-diagnostic and cannot assess features of malignancy accurately. Completeness of excision is assessed by gross pathological appearance and should be confirmed by formal histological examination[102]. In 80% of patients with MEN 1 who have endogenous hyperinsulinemia, there are multiple pancreatic tumors. In these patients, an 80%-85% subtotal pancreatectomy to the level of the portal vein with enucleation of lesions in the head of the gland is recommended to reduce the risk of exocrine and endocrine insufficiency. After successful surgical excision, overall 5-year survival has been 97% (5.96); the long-term survival is 88% at 10 years with a higher risk of recurrence in patients with MEN 1[5]. After resection, the risk of recurrence is greater in patients with MEN 1 (21% at 20 years) than those without MEN 1 (5% at 10 years and 7% at 20 years).

OCCULT INSULINOMA

Insulinomas continue to pose a diagnostic challenge to physicians, surgeons and radiologists alike. With the new preoperative localization techniques, especially the combination of biphasic thin-section helical CT and EUS resulted in an overall diagnostic sensitivity of 100%, very few cases of occult insulinoma may still be encountered. In the past, different strategies have been used to deal with this problem. Blind distal pancreatectomy, progressive pancreatectomy and subtotal pancreatectomy with intraoperative glucose monitoring have hitherto been recommended. Blind distal and progressive pancreatectomy are no longer indicated if no insulinoma is found, since recent studies indicate that occult tumors are more commonly located within the pancreatic head[13,42,43,100]. As insulinomas are small and the pancreatic head parenchyma is thick, most non-palpable tumors are in the pancreatic head. Intraoperative ultrasonography can play a critical role in the identification of non-palpable lesions. In a series by Norton[43], only 33% of insulinomas in the pancreatic head were palpable. However, intraoperative ultrasonography correctly identified 100% of them. Still, it is difficult to advocate performing a Whipple procedure on the basis of circumstantial evidence that the tumor may be present in the pancreatic head. If the tumor is not identified despite a careful exploration with intraoperative ultrasonography, termination of the operation without blind resection is recommended. In such cases the surgical procedure should be terminated, the abdomen should be closed, the patient referred to a specialist centre[13,42-44], and subjected to further investigation to verify the biochemical diagnosis and exclude factitious insulin administration. A repeat 72 h fast may be necessary to be certain of the diagnosis. A trial of the best current medical therapy to stabilize the patient on a short-term basis allows time for more extensive localization procedures applied before reoperation, often including the SAS intra-arterial calcium injection test[13,100], a technique that is useful in localizing the region of the pancreas containing the tumor. At re-exploration, if still no tumor is identified, the area of the pancreas suggested by the calcium angiogram should be removed. One might call this an enlightened resection rather than a blind resection.

MEDICAL MANAGEMENT

Medical management of insulinoma is generally restricted to high-risk candidates for surgery, those not suitable for resection or in those who have undergone an unsuccessful operation with persistent symptoms. Options include dietary management, diazoxide, calcium channel blockers and somatostatin analogues. Patients are advised to avoid prolonged fasting and to take frequent meals and snacks, including complex carbohydrates. The recommended daily dose of diazoxide is 200-600 mg orally. Good symptom control is achieved in about 50% of patients. However significant side effects of edema, weight gain, hirsutism and nausea are common. The calcium channel blocker, verapamil, has also been used with some success[102]. Octreotide, a synthetic somatostatin analogue results in only temporary and modest symptom relief. It can worsen hypoglycemic symptoms owing to a grater suppressive effect on growth hormone and glucagon secretion than on insulin. A satisfactory response is reported in only 50% of patients[5,128,129].

CONCLUSION

Insulinomas are uncommon tumors. Most are intra-pancreatic, benign and solitary. A biochemical diagnosis obtained during a supervised 72 h fast followed by high quality dual phase thin section multidetector CT of the pancreas and endoscopic ultrasound confirms the diagnosis and localize the insulinoma in the majority of patients and few cases of occult insulioma may persist. Intraoperative palpation and ultrasonography should enable accurate tumor localization if preoperative studies

fail to localize insulinoma. If the tumor still occult, blind pancreatic resection is not recommended. Laparoscopic treatment is increasingly performed, and leads to long term cure if the tumor is benign.

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