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Insulinoma

Aarti Mathur, MD[a], **Philip Gorden, MD**[b], and **Steven K. Libutti, MD, FACS**[c,d,e,*]

[a]Surgery Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, Building 10, Bethesda, MD 20892, USA

[b]Clinical Endocrinology Branch-NIDDK, National Institutes of Health, NIDDK, MSC 1612, 10 Center Drive, Bethesda, MD 20892, USA

[c]Montefiore-Einstein Center for Cancer Care, 3400 Bainbridge Avenue, Bronx, NY 10467, USA

[d]Albert Einstein Cancer Center, 3400 Bainbridge Avenue, Bronx, NY 10467, USA

[e]Department of Surgery, Montefiore Medical Center/Albert Einstein College of Medicine, Greene Medical Arts Pavilion, 4th Floor, 3400 Bainbridge Avenue, Bronx, NY 10467, USA

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Insulinoma is a rare neuroendocrine tumor with an incidence of 4 per 1 million persons per year.[1] Insulinoma may occur as a unifocal sporadic event in patients without an inherited syndrome or as a part of multiple endocrine neoplasia type 1. Key neuroglycopenic and hypoglycemic symptoms in conjunction with biochemical proof establish the diagnosis. Once the diagnosis is established, the insulinoma is preoperatively localized within the pancreas with the goal of surgical excision for cure. This review discusses the historical background, diagnosis, and management of sporadic insulinoma.

HISTORICAL BACKGROUND

Paul Langerhans, while a medical student, first described pancreatic islet cells in 1869.[2] Several decades later, in 1922, Banting and Best isolated insulin, or “isletin,” as they called it, from a solution extract of a dog's pancreas. One year later, in 1923, Harris suggested a clinical possibility of hyperinsulinism and contrasted it with the hypoinsulinism of diabetes.[2] His suspicion was confirmed the following year, when several case reports of patients with symptomatic hyperinsulinism were published.[2]

However, it was not until 3 years later that the association between hyperinsulinism and a functional islet cell tumor was first established by Wilder and colleagues[3] after he performed an operation in a patient with hypoglycemia and found an islet cell carcinoma with hepatic metastases. The first surgical cure of an islet cell tumor was achieved by Graham in 1929.[2] Several years later, Whipple observed that symptoms of hypoglycemia provoked by fasting, a circulating glucose level of less than 50 mg/100 mL when these symptoms presented, and relief of these symptoms with administration of glucose was the basis for the diagnosis of an insulinoma, thus establishing the “Whipple triad” that we now use today.[2]

*Corresponding author. slibutti@montefiore.org (S.K. Libutti)..

SPORADIC VERSUS MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Insulinoma can occur sporadically, or it can be associated with multiple endocrine neoplasia type 1 (MEN-1). MEN-1 syndrome is an autosomal dominant condition that occurs as a result of inactivating mutations of the MEN1 gene located on chromosome 11.[4] This syndrome is characterized by primary hyperparathyroidism, anterior pituitary adenomas, and tumors of the endocrine pancreas and duodenum. The most common functioning islet cell tumors in MEN-1 are gastrinomas and insulinomas.[4]

Insulinoma affects approximately 10% of MEN-1 patients.[4] In contrast to sporadic insulinomas, which typically present as solitary, benign, encapsulated lesions, MEN-1 associated insulinomas develop earlier and tend to be multifocal, occurring throughout the pancreas.[5,6] This review focuses on the diagnosis, localization, and management of sporadic insulinomas.

DIAGNOSIS

As described by “Whipple's triad,” hypoglycemia and neuroglycopenic symptoms that are corrected by the administration of carbohydrate are the hallmarks of the diagnosis of insulinoma. Inappropriately elevated insulin levels cause hypoglycemic episodes characterized by neuroglycopenic symptoms and sympathetic overdrive (Table 1). These symptoms are typically precipitated by fasting or exercise, but can also occur postprandially, or have no relationship to eating.[7]

Neuroglycopenic symptoms vary in spectrum and include difficulty awakening, visual disturbances, confusion, lethargy, weakness, abnormal behavior, seizures, loss of consciousness, or coma.[7,8] In addition, hypoglycemia also results in catecholamine release with adrenergic sympathetic nervous system activation resulting in sweating, anxiety, and palpitations.[7,8] Erroneous psychiatric or neurologic diagnoses are common in this situation, resulting in a delayed diagnosis.

The diagnosis of insulinoma can only be established by documenting symptomatic hypoglycemia with inappropriately elevated insulin levels during a 48-hour monitored fast (Fig. 1).[9] Hypoglycemia is defined as a blood sugar level less than 50 mg/dL in the fasting state. In healthy individuals, the blood glucose level does not fall below 70 mg/ dL after an overnight fast.[10] For many years, well before tests for determination of insulin and proinsulin were readily available, the 72-hour monitored fast was the cornerstone for diagnosis. However, in more than 97% of individuals, a supervised fast of 48 hours in conjunction with biochemical testing, including plasma insulin and proinsulin measurements every 6 hours, is sufficient to diagnose insulinoma.[11] In addition, patients with this diagnosis typically have serum insulin levels higher than 5 to 10 μU/mL and an insulin to glucose ratio greater than 0.3.[9] In obese patients with peripheral insulin resistance, these values may be elevated and mimic the pattern of an insulinoma.[9]

Other conditions may cause fasting hypoglycemia with elevated insulin levels.[10] These conditions include pancreatic islet disease other than insulinoma, and factitious use of excessive insulin or hypoglycemic agents. To differentiate from these conditions, tests such as a plasma proinsulin, C peptide, sulfonylurea must be used. Endogenous insulin is synthesized as a precursor, proinsulin, which can be quantified. Proinsulin values are poorly suppressible in these patients in contrast to noninsulinoma patients.[12] Eighty-seven percent of patients with insulinoma have a plasma proinsulin component equal to or greater than 25% of the total immunoreactive insulin or specific proinsulin concentration of 22 pmol or more. In patients with surreptitious use of insulin or an oral hypoglycemic agent, the proinsulin level is either normal or decreased.

During the body's production of insulin C-peptide is cleaved from proinsulin, making it another useful indicator of surreptitious insulin use. Commercial insulin preparations do not contain it. Therefore, an elevated C-peptide indicates endogenous hyperinsulinism.

In summary, key neuroglycopenic and sympathetic symptoms together with biochemical proof establish a diagnosis of insulinoma. To diagnose an insulinoma, in addition to documenting blood glucose levels below 50 mg/dL during monitored symptomatic episodes that improve with oral intake, the patient should have elevated C-peptide levels (>200 pmol/L) and absence of plasma sulfonylurea. Box 1 shows the common diagnostic criteria for insulinoma.

LOCALIZATION

After establishing a diagnosis of insulinoma, a variety of imaging modalities with different sensitivities can localize the tumor. The role of preoperative imaging is 2-fold. First, imaging is used to evaluate for evidence of metastatic disease; second, localization can better facilitate discussions with the patient with regard to extent and type of operation. Because virtually all sporadic insulinomas are small and intrapancreatic, preoperative localization fails 10% to 27% of the time.[13] The extent of imaging necessary to ensure an operative cure has not been clearly defined and varies between institutions. In fact, some suggest that preoperative localization within the pancreas is not even necessary because the insulinoma can be localized successfully intraoperatively.[14]

Results of noninvasive localization studies, including transabdominal ultrasound, multiphase helical computed tomography (CT), magnetic resonance imaging (MRI), and somatostatin receptor scintigraphy (SRS) are disappointing. The success rate of transabdominal ultrasound for localization varies widely across institutions, from 9% to 66%.[7,13,15–17] Multiphase helical CT localizes 50% to 80% (Fig. 2), MRI 40% to 70%, and SRS 17% of all insulinomas.[7,13,15–19] All of the these imaging studies combined can localize around 80% of tumors.[13,16,17] CT and MRI are useful to evaluate for metastatic disease, although MRI may be more sensitive than CT in identifying liver metastases.[9]

When preoperative noninvasive studies fail to localize tumors, invasive studies may aid in regional localization. Pancreatic arteriography was historically considered the gold standard, with early reports quoting success rates of 90%.[13] However, more recent studies show a much lower rate of localization in the range of 25% to 50%.[7,13,15–17]

Transhepatic portal venous sampling (THPVS) involves percutaneous and transhepatic catheterization of a branch of the portal vein followed by advancement into the small draining veins of the pancreas, including the superior mesenteric, portal, and splenic veins, to sample blood for insulin.[13,20] A step-up in the insulin level reflects the region of the pancreas where the insulinoma resides. This technique has shown a 77% to 100% success in localization.[17,20,21] However, THPVS requires special skills and experience and is associated with slight, but significant morbidity; it has therefore been abandoned.

THPVS has been replaced by intra-arterial calcium stimulation (IAC), which relies on calcium as a secretagogue for insulin secretion from the tumor.[15,16] IAC involves catheterization of the gastroduodenal, superior mesenteric, and proximal and distal splenic arteries, which are then subsequently injected with calcium.[15,16] Blood is sampled for insulin from a second catheter, which is placed first in the right hepatic vein and then the left hepatic vein for corroboration. A step-up in the insulin concentration localizes the insulinoma to a particular region of the pancreas (Figs. 3 and 4). IAC has a reported sensitivity from 80% to 94% in localizing insulinomas to a particular region of the pancreas.[15,16]

The use of endoscopic ultrasound for tumor localization has steadily increased over the past several years. Reported sensitivities range from 40% to as high as 93%.[21,22] The sensitivity has shown to vary by tumor location, and is also operator dependent. The authors' experience with endoscopic ultrasound is limited, as this modality is not employed at our institution.

The use of intraoperative ultrasound (IOUS), introduced in 1981, is useful to localize intrapancreatic, nonpalpable lesions, and to determine the proximity of those lesions to the pancreatic or biliary duct. IOUS performed during an open or laparoscopic exploration can localize an insulinoma in 86% of cases.[16,21]

The practice at the authors' institution once the diagnosis of insulinoma has been made is to obtain a CT scan to evaluate for metastatic disease and to assist with localization of the lesion. If the CT scan successfully localizes the lesion, the patient is taken to the operating room for either an open or laparoscopic exploration with IOUS. If the CT scan does not show a lesion, the patient undergoes intra-arterial calcium stimulation to regionalize the tumor, then is taken to the operating room.

MANAGEMENT

Medical Management

For patients who are not surgical candidates or those who are waiting for an operation, several measures can be taken to manage the symptoms, including dietary modification and pharmacologic agents. Dietary modification includes consumption of frequent, small meals throughout the day and middle of the night to avoid symptomatic hypoglycemia. The initial drug of choice, and the most well studied, is diazoxide, a benzothiadiazide. Diazoxide directly inhibits insulin release from β cells via stimulation of α-adrenergic receptors. Diazoxide also inhibits cyclic adenosine monophosphate phosphodiesterase (cAMP), which enhances glycogenolysis and has a hyperglycemic effect. Initiation doses of 150 to 200 mg given in 2 to 3 divided doses per day should be titrated to maximum dose of 400 mg daily. Diazoxide offers symptom control in about 50% to 60% of patients.[7] Sodium retention and edema, which occur in about 50% and may require addition of a diuretic, complicate the use of diazoxide. Gastrointestinal symptoms such as nausea, and occasional hirsutism, can also occur.

The somatostatin analogues octreotide and lantreotide bind with high affinity to the second of the 5 subtypes of the somatostatin receptor, sst2.[23,24] This receptor is present in varying degrees on insulinomas, accounting for the variability of response. However, this class of agents can decrease plasma insulin levels and alleviate symptoms in 40% to 60% of patients.[23,24] Initiation doses of 50 μg subcutaneously 2 or 3 times daily may be increased to 1500 μg daily. Major side effects include gastrointestinal bloating, abdominal cramping, malabsorption, and cholelithiasis.[23,24] Octreotide can also decrease glucagon and growth hormone levels, resulting in a worsening hypoglycemia in some patients. The mean duration of octreotide treatment in studies is 1 year and frequently tachyphylaxis develops.[8]

Phenytoin (Dilantin), at a maintenance dose of 300 to 600 mg daily, inhibits the release of insulin from β cells and has been used to treat a small number of patients with insulinoma.[8,9] Only in about one third of the patients does a clinically significant hyperglycemic effect occur. Verapamil, a calcium channel blocker, and propranolol, a β-blocker, have been used in a few patients either alone or in combination with other drugs to help control symptoms.[8,9] Glucocorticoids and glucagon have also been given alone or in conjunction with diazoxide to a few patients, with some palliation achieved.[9]

Surgical Management

Most sporadic insulinomas are benign, solitary lesions that are amenable to complete surgical excision for cure. At surgical exploration, the entire abdomen is inspected for evidence of metastatic disease or extrapancreatic tumors that secrete insulinoma-related growth factors.[9] Next, the entire pancreas is exposed to palpate any tumors.

Palpation of the pancreas effectively localizes the insulinoma 70% of the time. Next, intraoperative ultrasound, which has an 86% rate of detection, is performed. Intraoperative detection of an insulinoma with the combination of palpation and ultrasound ranges from 83% to 98%.[17,25] In addition, IOUS also allows identification of the pancreatic duct and vessels and determination of the proximity of the tumor to these structures.

Because most insulinomas are benign, tumor enucleation is the procedure of choice, when possible.[26,27] Insulinomas tend to be compact and encapsulated, presenting a clear dissection plane between the tumor and the surrounding pancreas (Fig. 5). It is important to remove the tumor with the capsule completely to prevent a local recurrence. A segmental resection of the pancreas, distal pancreatectomy, or rarely a pancreaticoduodenectomy, may be required for lesions in close proximity to the pancreatic duct or involving a large portion of the pancreatic substance. Tumors that are hard, infiltrating, create puckering of surrounding tissue, or cause pancreatic duct dilation should raise a suspicion of malignancy, and therefore also be removed by formal resection.

Historically, if the tumor could not be localized intraoperatively, blind distal pancreatectomy would be performed. However, because insulinomas may occur throughout the pancreas with relatively equal frequency, a blind distal pancreatectomy for an occult tumor is an inadvisable procedure.[28] In addition, with the current status of localization studies this practice is largely unnecessary.

With the recent advances in laparoscopic technique and instrumentation, the surgical management of an insulinoma has moved toward a minimally invasive approach. Laparoscopic ultrasound detects 86% of insulinomas.[21] Some institutions also favor placing a handport for palpation to aid in detection.[29] Laparoscopic resection is successful in 70% to 100% of cases.[29,30] However, it is still performed in only a minority of cases.

Complications related to the actual pancreatic procedure are similar for both the open and laparoscopic approach, and are as high as 45%.[29–31] Pancreatic duct leak causing pseudocyst, abscess, or fistula formation comprise the main source of this morbidity. Rates of pancreatic fistula are reported to be 15% to 43%.[26,29,31] Fernandez-Cruz and colleagues[29] noted a higher incidence of pancreatic fistula after enucleation than with distal pancreatectomy and splenectomy (38% vs 12.5%). Most these fistulas can be managed conservatively with drainage, parenteral nutrition, and somatostatin analogues to decrease the output. Some may require placement of a stent in the pancreatic duct or rarely, reoperation. Intra-abdominal abscess requiring percutaneous drainage occurs at a rate of 4% to 6% postoperatively, and 4% to 8% patients develop temporary delayed gastric emptying, which can be managed with pharmacologic agents.[17,29,32]

METASTATIC DISEASE

The documentation of metastatic disease, either at the time of surgery or by imaging studies, is the only accurate means of diagnosing a malignant insulinoma. Metastases predominantly present in the liver or lymph nodes but can also be found in the bone and peritoneal tissue, resulting in uncontrolled insulin secretion.[33,34] Life-threatening and debilitating hypoglycemia can occur from these hormone active lesions.[33,35,36] Achievement of

glycemic control becomes critical and pharmacologic palliation with diazoxide, octreotide, or glucagon must be used.[36]

In a retrospective review, Danforth and colleagues[37] found that primary malignant tumors were usually single, with a mean diameter of 6 cm. These investigators reported median disease-free survival of 5 years with recurrence rate of 63% at a median of 2.8 years after curative resection.[37] However, the clinical course of patients with metastatic disease is variable. Some patients with indolent tumors may remain symptom-free for years without treatment, whereas others have symptomatic disease progression from hypersecretion of insulin or tumor bulk.[36] Long-term survival is not unusual, and 25% to 35% of patients may survive longer than 5 years.[33,36] After initial tumor resection, the biology of the tumor rather than any treatment modality most likely determines long-term survival.[33]

Because malignant insulinomas are rare, occurring in only 5% to 15% of all reported cases, controlled studies that address a specific therapeutic approach to treatment have not been performed and are probably not feasible.[33,34,38] Affected patients usually are included with other neuroendocrine tumor patients on various protocols intended to evaluate the effectiveness of a particular therapy. Despite the various therapies including surgery, chemotherapy, biotherapy, hepatic embolization, hepatic perfusion, radiofrequency ablation, and peptide-receptor radionuclide therapy, prognosis remains poor with a median survival of approximately 2 years.[25]

Surgery

The goals of surgery are to maximize local control and minimize hypoglycemic symptoms to improve quality and duration of patient survival. Cytoreductive surgery can alleviate symptoms in metastatic insulinoma in a select group of patients. Patients with a reasonable performance status, with minimal extrahepatic disease, and whose primary tumor has been or can be removed, are candidates for cytoreductive surgery. The current mortality rate of less than 2% and major morbidity rate of less than 20% represent the success of the operative approach and justify this intervention.[38–41] Unfortunately, however, curative cytoreduction is possible in less than 10% of all patients with metastatic insulinoma.[36,42,43]

A large retrospective study of 170 patients with neuroendocrine tumors, consisting of 108 patients with hormonally active tumors and 18 patients with functional islet cell tumors, reported a 95% biochemical response that lasted for a median of 45 months.[39] Overall survival for 170 patients was 61% and 35% at 5 and 10 years, respectively.[39] However, disease recurrence was 85% at 5 years.[39] Recently, Osborne and colleagues[44] reported the first series of 120 patients comparing embolization to curative or palliative resection. In patients who underwent cytoreduction, complete and partial symptomatic relief was achieved in 69% and 23%, respectively, compared with 59% and 32% in the embolization group.[44] The cytoreduction group had a statistically significantly longer mean duration of symptom relief (35 ± 22 months vs 22 ± 13.6 months), and increased mean survival (43 ± 26 months vs 24 ± 16 months).[44] The curative cytoreduction group had an increased survival compared with the palliative cytoreductive group (50 ± 27.6 months vs 32 ± 18.9 months).[44] Several other single-institution studies have reported 5-year survival benefit from 60% to 70% after curative resection; however, this benefit has yet to be proven in randomized clinical trials.[34,36,38–40]

Hepatic transplantation—For clearly unresectable liver metastases, there has been some limited experience with hepatic transplantation. An early report on liver transplantation for 30 patients with metastatic gastroenteropancreatic neuroendocrine tumors showed a 1-year survival of only 52%.[45] However, a later review of 103 patients reported a 2-year and a 5-year survival rate of 60% and 47%, respectively.[46] In 2002, the largest, single-center study

of liver transplantation for gastroenteropancreatic neuroendocrine tumors consisting of 19 patients reported a 5-year survival of 80%.[45] Patients younger than 50 years old, who have had their primary pancreatic tumor completely resected and have no extrahepatic disease, tend to have a more favorable prognosis.[45] Various other studies report 5-year survival after liver transplant for neuroendocrine tumors in the range of 36% to 80%.[47,48] In addition, the aforementioned studies included carcinoid tumors, which also portend a better prognosis with transplantation. Given the morbidity of this procedure and the questionable survival benefit, hepatic transplantation may be considered in highly selected patients and should still be considered investigational.

Biotherapy with Octreotide/Interferon

Biotherapy with somatostatin analogues is frequently instituted in patients with enlarging tumor burdens, especially in slow-growing neuroendocrine tumors without extensive liver involvement. Proposed mechanisms include inhibition of endocrine growth factors, such as insulin-like growth factor-1, direct binding of somatostatin receptors, and antiangiogenic properties.[9,36,49] Octreotide can also inhibit endothelial cell proliferation through somatostatin receptors present on endothelial cells.[9] Studies suggest that this drug is well tolerated and has mostly a tumoristatic effect, causing a decrease or cessation of growth in 30% to 80% of patients with neuroendocrine tumors.[8] Objective tumor responses are typically less than 10% with a median duration of 7 months.[50] The presumption that a tumoristatic effect will result in improved progression free or overall survival has yet to be clearly demonstrated. Somatostatin analogues must be used with caution in patients with metastatic insulinoma, as these tumors frequently do not express the sst2 receptor to which this drug binds.[24,30,33,50] In addition, inhibition of glucagon may worsen hypoglycemia.

Interferon has been extensively studied in low-grade neuroendocrine tumors and a small proportion of pancreatic neuroendocrine tumors (PNETs).[8,13,36,51] The exact mechanism of action is unclear at this time, but similar to octreotide, its major effect is tumor growth stabilization rather than inducing regression.[34] Interferon-α at doses of 5 to 6 million units given 3 to 5 times weekly has shown a radiological response in less than 20% patients with PNETs.[8,36] Unfortunately, interferon causes a multitude of side effects including flulike symptoms, fatigue, weight loss, lipid, thyroid, and liver function abnormalities, and overall is not well tolerated by most patients.[8,13,36,51] Combination treatments with interferon with somatostatin remain investigational.[52]

Chemotherapy

Systemic chemotherapy for advanced or metastatic pancreatic endocrine tumors has been studied with various single as well as combinations of agents over the past 3 decades. In general, responses range from 6% to 69%, with median overall survival ranging from 17 to 38 months with chemotherapy.[36,41,53–55]

Streptozocin was approved by the Food and Drug Administration (FDA) in 1976 for use in PNETs after a 50% response rate was observed among 52 patients who were treated.[13] Subsequent studies have shown response rates of 36% to 50% with limited duration. In addition, patients suffer significant nausea, vomiting, and renal and hematological toxicity.[8] Doxorubicin has also demonstrated single-agent activity with a response rate of 33% in a phase II trial that included 42 patients.[8,9,36]

Combination chemotherapy consists of various streptozocin-based regimens allowing for the use of smaller doses of streptozocin to reduce toxicity. The Eastern Cooperative Oncology group compared 5-fluorouracil (5-FU) with streptozocin to streptozocin with doxorubicin to chlorozotocin monotherapy, and found response rates of 45%, 69%, and 30%,

respectively.[53] In addition, compared with the streptozocin with 5-FU, the streptozocin with doxorubicin showed an increased median time to progression (20 months vs 7 months), increase median overall survival (2.2 years vs 1.4 years), and a mean duration of response of 18 months.[53]

Because response criteria used in older studies was not standardized, the reported response rates may be exaggerated. Two more recent retrospective studies show response rates of 6% after combination of streptozocin and doxorubicin.[41,55] In the largest series of 84 patients treated with combination streptozocin, doxorubicin, and 5-FU, the response rate was 39%, median progression free survival 18 months, and median overall survival 37 months.[54] That study showed a median time to response of 4 months, indicating that patients who do not have disease progression should be continued on this regimen for at least 4 months.[54]

Temozolamide, an oral alkylating agent, has been studied in combination with several other agents. In a phase II trial, temozolamide plus thalidomide showed a response rate of 45%.[56] Temozolamide with bevacizumab, a vascular endothelial growth factor inhibitor, showed a response rate of 24% among 17 PNETs treated.[9] Temozolamide in combination with capecitabine showed a response rate of 59% among 17 patients with metastatic neuroendocrine tumors of the pancreas.[9]

Several novel therapies are now available that are directed at multiple various growth factors produced by these tumors. These treatments include the tyrosine kinase inhibitors, sutinib and imatinib, with response rates of 17%, as well as agents targeting downstream targets of tyrosine kinase receptor activation, such as mammalian target of rapamycin, a threonine kinase involved in regulating cell cycle progression.[8] Despite the multitude of publications, the role of cytotoxic chemotherapy continues to be debated. At this time, due to lack of randomized controlled trials, which are difficult to perform because of the rarity of these tumors, it is unclear which chemotherapy regimen is best.

Liver-Directed Therapy

Hepatic artery embolization, chemoembolization, and infusion—Hepatic artery embolization (HAE) takes advantage of the liver's dual blood supply. The normal liver derives most of its blood supply from the portal circulation, whereas metastatic lesions derive most of their blood supply from the hepatic artery. Therefore, interruption of the hepatic artery preferentially causes ischemic necrosis of hepatic metastases while preserving normal liver. The generally accepted indications for embolization in patients with neuroendocrine tumors metastatic to the liver include unresectable disease producing symptoms related to either hormonal excess or tumor bulk, or rapid disease progression.

At present a variety of small particles are available to occlude the hepatic artery including lipiodol or ethiodized oil, a cottonseed oil-based contrast material, small plastic particles, and gelatin foam particles.[8] Comparative studies among these agents are lacking. Hepatic arterial vascular occlusion for islet cell carcinomas has produced objective tumor responses in 17% to 82%.[42]

Addition of chemotherapy to the embolic material, or hepatic artery chemoembolization (HACE) has several theoretical advantages. Regional delivery of chemotherapy can offer pharmacokinetic advantages and may increase intratumoral drug concentration as well as time of exposure. In addition, certain chemotherapeutic agents such as doxorubicin, mitomycin C, and streptozocin are more active in hypoxic tumor cells.[42,49] Small series have reported biochemical response rates 47% to 91% and tumor response rates that vary across the board from 0% to 100%.[42,44,49] Median survival ranges from 9 to 20 months for islet cell carcinomas in various studies.[42] Although several studies have established

beneficial therapeutic effects of HAE and HACE, it is unclear whether chemoembolization confers therapeutic advantage over bland embolization.

Hepatic artery infusion (HAI) involves administration of high-dose chemotherapy with streptozocin or 5-FU via the left, right, or main hepatic artery.[34,57] This procedure is usually followed up by HACE. In a small series of patients treated with 4 monthly cycles of 5-FU, median response rate for patients with functional PNETs was 91% with median survival of 46 months. Response rates for HAI range from 0% to 100% for islet cell neoplasms in various studies.[34,49,57]

Isolated hepatic perfusion (IHP) is a regional treatment strategy that requires a laparotomy to completely isolate the vascular supply of the liver, permitting hepatic perfusion with high-dose chemotherapy using an extracorporeal perfusion circuit (see Fig. 1).[58–60] The perfusion circuit provides inflow with chemotherapeutic agents via the gastroduodenal artery and receives outflow from the suprarenal and retrohepatic inferior vena cava (IVC). Systemic blood flow is maintained by venovenous bypass from the infrarenal IVC, cannulated via a saphenous vein cut down to the left axillary vein.[58–60] Separation of the hepatic and systemic circulation permits usage of higher doses of chemotherapy, administration of agents such as tumor necrosis factor (TNF), and allows for manipulation of various conditions such as hyperthermia or hypoxia. IHP with melphalan or melphalan and TNF in patients with progressive liver metastases from pancreatic and gastric neuroendocrine tumors has shown a response rate of 50%, with a mean duration of 15 months.[60] The major disadvantage of this approach is that only a single treatment can be applied and it requires an open surgical procedure with associated morbidity.[61]

Percutaneous hepatic perfusion evolved from IHP as a minimally invasive approach allowing multiple treatments with the same principles as an open hepatic perfusion.[61] The procedure requires cannulation of bilateral internal jugular veins and the common femoral artery while the patient is under general anesthesia. Complete vascular isolation is accomplished using a double balloon IVC catheter system (Delcath Systems, New York, NY), placed percutaneously.[61] Melphalan is infused directly into the hepatic artery. Hepatic venous outflow is collected via the double balloon catheter, which sits in the retrohepatic IVC, and is run through a pair of activated charcoal filters before returning to the systemic circulation by a catheter in the internal jugular vein. In a phase I study of hepatic arterial melphalan infusion with hepatic venous hemofiltration, a 30% response rate was observed.[61] A phase II trial is currently under way.

Ablative techniques—Patients may occasionally have too many small lesions to be considered resectable; however, they may be candidates for an ablative approach. Radiofrequency ablation (RFA) destroys tumors by heat. A probe is inserted directly into the tumor during laparoscopy or laparotomy, or percutaneously with image guidance. This probe emits high-frequency radio waves that generate frictional heat from ionic vibration of tissue particles. This thermal energy produces temperatures higher than 60°C, resulting in coagulation necrosis of the tumor.[62] The symptomatic response rate to RFA ranges from 71% to 95% that lasts for a mean duration of 8 to 10 months.[62] In one of the largest series, new liver lesions developed in 28% of patients at a mean of 1.6 years and local liver recurrence was reported to be 13%.[63]

Cryoablation is similar to RFA, with the exception that it relies on freezing as the method of tumor destruction. A probe inserted into the tumor passes liquid nitrogen into the tumor, subjecting it to multiple freeze and thaw cycles. Although RFA is used more commonly today, there are small series in the literature that report cryoablation as an effective approach.[8]

Percutaneous ethanol injection (PEI) can be incorporated for treatment of liver metastases from neuroendocrine tumors. In one study, complete responses were observed in all 4 neuroendocrine hepatic metastases.[64] Others have performed PEI of metastases located adjacent to vital structures such as the hepatic flexure of the colon, metastases adjacent to large vessels vulnerable to the heat-sink effect, and metastases adjacent to central bile ducts, where subsequent biliary stricture may occur.[65] Various studies have shown that complete necrosis of liver metastases can be obtained. This technique is usually employed for hepatocellular carcinoma and is not effective for metastatic PNETs. PEI has largely been replaced by radiofrequency thermal ablation and cryoablation.[66]

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) is an emerging treatment modality for patients with unresectable, somatostatin-receptor positive neuroendocrine tumors. This treatment relies on the fact that some insulinomas express somatostatin receptors and internalize radiolabeled analogues, facilitating delivery of cytotoxic doses of localized radiation to the tumor. With this approach roughly 25% patients had an objective tumor response, with greater than 50% shrinkage.[67,68] Over the past decade, the most frequently used somatostatin analogues intravenously injected include indium-111 (^{111}In), yttrium-90 (^{90}Y), and lutetium-177 (^{177}Lu).[67] Whereas complete responses are rare, partial response rates vary from 0% to as high as 40% with a median duration ranging from 12 to 37 months. Side effects include hematologic toxicity and renal toxicity, which can be reduced by coadministration of amino acids. This form of therapy is currently under evaluation at several centers to further define its utility.

Selective Internal Radiation Therapy

There has been considerable interest in 2 radioactive microsphere devices recently approved by the FDA for liver-directed therapy. TheraSphere (MDS Nordion, Ottawa, Canada), which consists of nonbiodegradable glass microspheres, is FDA approved for unresectable hepatocellular carcinoma. SIR-Spheres (Sirtex, Wilmington, MA) consists of resin microspheres and is approved for metastatic colon cancer to the liver. Both devices contain ^{90}Y. The principle underlying this technology is the preferential distribution of microspheres via direct hepatic transarterial injection into the peritumoral vasculature, allowing delivery of high doses of radiation into the tumor and sparing normal liver. Selective internal radiation therapy with ^{90}Y microspheres has been used to treat hepatic metastases from neuroendocrine tumors in a limited number of patients. A recent study of 84 patients who received a tumor dose of 1000 Gy reported stable disease in 67% of patients for 12 months, symptomatic palliation in 80%, and few responses.[62,69] King and colleagues[69] reported a symptomatic response rate of 50% at 6 months with 18% complete tumor responses, 32% partial responses, and mean overall survival of 29.4 3.4 months. Further investigation of the agents will help delineate its role in metastatic neuroendocrine tumors.

SUMMARY

Insulinoma is a rare, usually benign, pancreatic islet cell tumor. A patient with a suspected insulinoma should undergo a monitored 48-hour fast with appropriate confirmatory laboratory values to establish the diagnosis. Next, a CT scan is carried out evaluate for metastatic disease as well as to localize the lesion within the pancreas. If CT is unable to localize the lesion, intra-arterial calcium stimulation to regionalize the tumor is recommended.

The patient is then taken to the operating room for either an open or laparoscopic exploration with intraoperative ultrasound. Because most insulinomas are solitary and benign, enucleation, if feasible, is the procedure of choice. However, a tumor in close proximity to the pancreatic duct, a large or hard tumor creating puckering of the surrounding tissue requires a formal resection. Medical management, including diazoxide, should be initiated while awaiting surgical excision to temporize symptoms.

On rare occasions patients present with metastatic disease, most commonly to the liver and lymph nodes. In patients with metastatic disease surgical debulking, if possible, provides long-term survival. However, if surgical resection is not possible then other options exist. For hepatic predominant disease, treatments such as RFA, HAE, chemoembolization, and hepatic perfusion may be used. Other potential treatment options for metastatic disease include cytotoxic chemotherapy, molecularly targeted therapy, or targeted radiotherapy. Because of the infrequent occurrence of metastatic insulinoma, prospective randomized trials have not been conducted to evaluate the superiority of these therapies.

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Box 1 Common diagnostic criteria for insulinoma

Documentation of blood glucose of <50 mg/dL with hypoglycemic symptoms

Relief of symptoms after eating

Elevated C-peptide (>200 pmol/L)

Absence of plasma sulfonylurea

Increased serum insulin level (>5–10 μU/mL)

Increased proinsulin level (≥25% or ≥22 pmol)

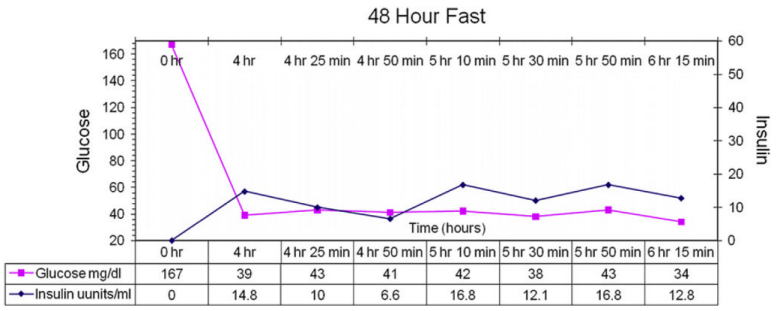


Fig. 1.

Forty-eight hour fast. This patient has elevated serum insulin levels (>10 μU/mL) despite hypoglycemia indicating an insulinoma. (*Courtesy of* National Institutes of Health, Bethesda, MD).

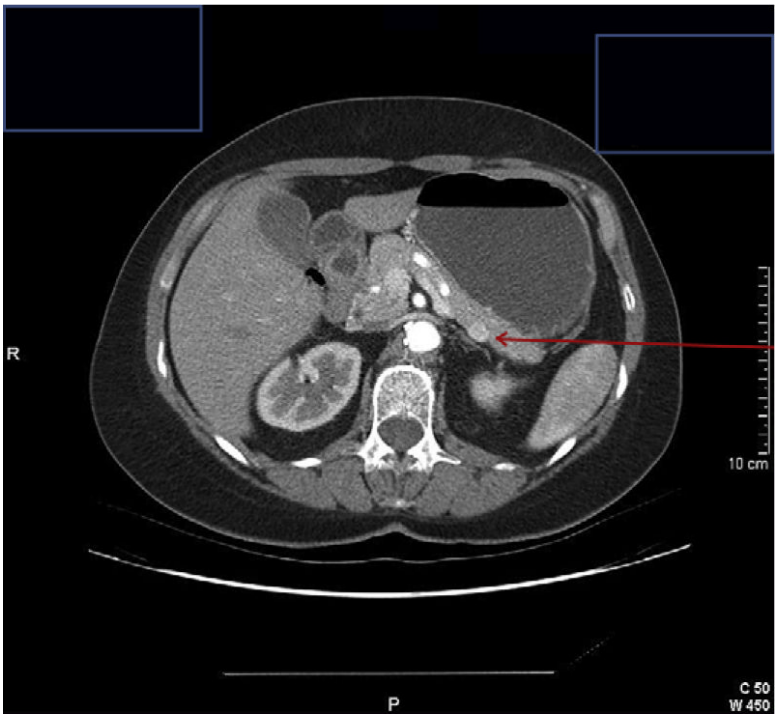
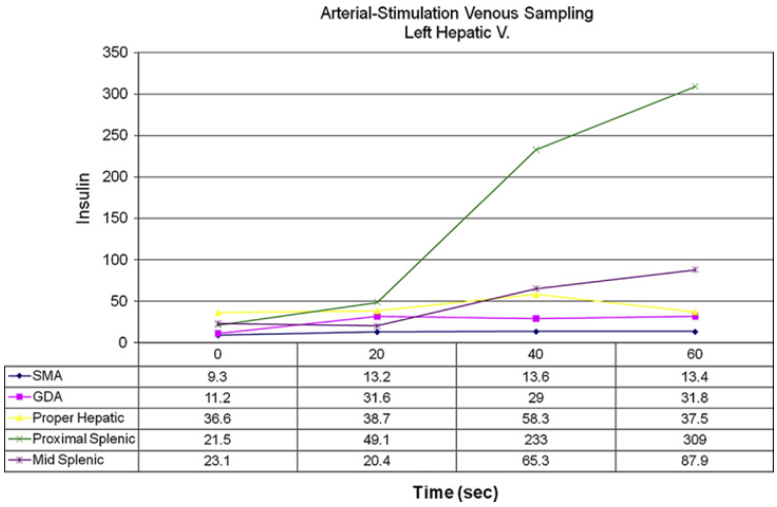


Fig. 2.

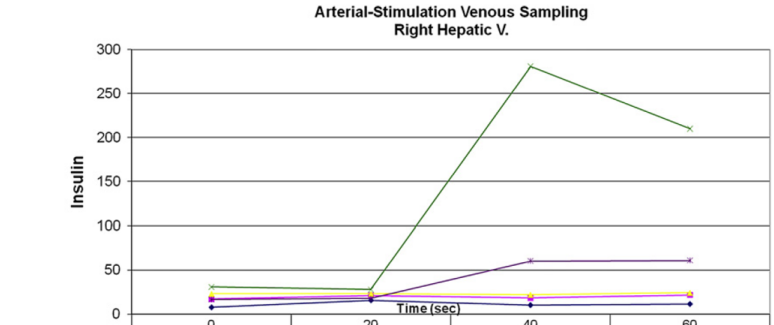
Lesion successfully localized by computed tomography scan. A round, well-circumscribed, hyperenhancing lesion can be seen at the tail of the pancreas (*arrow*). (*Courtesy of* National Institutes of Health, Bethesda, MD.)



	0	20	40	60
SMA	9.3	13.2	13.6	13.4
GDA	11.2	31.6	29	31.8
Proper Hepatic	36.6	38.7	58.3	37.5
Proximal Splenic	21.5	49.1	233	309
Mid Splenic	23.1	20.4	65.3	87.9

Fig. 3.

Left hepatic vein insulin concentrations after intra-arterial calcium injection. Injections of the superior mesenteric artery (SMA), gastroduodenal artery (GDA), and proper hepatic artery do not show any suspicious areas. However, the increase in insulin concentration after injection into the proximal and mid splenic arteries help localize this lesion to the tail of the pancreas. (*Courtesy of* National Institutes of Health, Bethesda, MD.)



	0	20	40	60
SMA	7.8	15.6	10.3	11.5
GDA	17.2	21.2	18.5	21.7
Proper Hepatic	23	23.1	22	24.2
Proximal Splenic	31	28.1	281	210
Mid Splenic	16.8	17.7	60.4	61

Fig. 4.

Right hepatic vein insulin concentration after intra-arterial calcium injection. Injections of the SMA, GDA, and proper hepatic artery do not show any suspicious areas. However, the increase in insulin concentration after injection into the proximal and mid splenic arteries helps to localize and confirm that this lesion is in the tail of the pancreas. (*Courtesy of* National Institutes of Health, Bethesda, MD.)

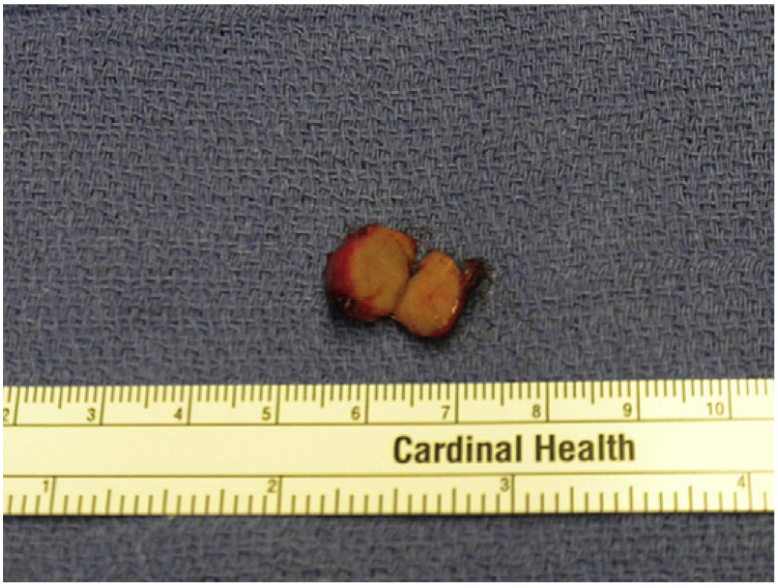


Fig. 5.
Insulinoma enucleated from the tail of the pancreas. (*Courtesy of* Steven K. Libutti, MD, Bethesda, MD.)

Table 1

Symptoms and frequency of clinical symptoms[7,8]

Neuroglycopenic Symptoms	
Visual disturbances	59%
Altered mental state ± confusion	75%–80%
Coma or amnesia	47%
Abnormal behavior	36%
Weakness	24%–32%
Seizures	17%–23%
Sympathetic Adrenergic Symptoms	
Palpitations	10%–12%
Sweating	12%–69%
Tremors	17%–24%
Hyperphagia/obesity	25%–50%