

Detection of insulinoma using ⁶⁸Gallium-DOTATATE PET/CT: a case report

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Abstract: Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia in non-diabetic adults. They are most often benign, small and difficult to localize with current imaging techniques. This is of high importance, as complete surgical resection is the only curative treatment. Anatomic imaging, ¹¹¹In-pentetreotide scan and ⁶⁸Gallium-DOTATATE positron emission tomography/computed tomography (PET/CT) were compared in a patient with insulinoma. ⁶⁸Gallium-DOTATATE PET/CT and selective arterial calcium stimulation localized the insulinoma. At surgery, a tumor in the anterior aspect of the pancreatic body was found which confirmed the preoperative localization, and a 2.1 cm tumor was enucleated, World Health Organization (WHO) grade I insulinoma. The patient remains euglycemic and free of symptoms at last follow up. In conclusion, ⁶⁸Gallium-DOTATATE PET/CT imaging may be a useful adjunct localizing study for insulinomas. It is a non-invasive preoperative localization study that could guide surgical exploration for successful therapy.

Keywords: Insulinoma; ⁶⁸Gallium-DOTATATE; neuroendocrine tumor (NET); positron emission tomography (PET)

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Introduction

Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia in nondiabetic adult patients, with an incidence of 1-3 per million per year (1). They are most commonly localized in the pancreas and approximately 85% are solitary, 6-13% are multiple and 4-6% are associated with multiple endocrine neoplasia type 1 (1,2). More than 90% of insulinomas are benign.

The clinical features of insulinoma result from hypoglycemia and autonomic nervous overactivity. Patients may present with the Whipple triad: symptoms of hypoglycemia, low blood glucose (40-50 mg/dL), and relief of symptoms after the administration of glucose (3). The gold standard for the diagnosis of insulinoma is a 48-hour supervised fast when the insulin/proinsulin

levels are inappropriately high for a glucose level below 40 mg/dL with negative levels for beta-hydroxybutyrate and sulfonyleurea and using a point of discrimination for proinsulin of ≥ 22 pmol/L (4). Seventy-nine percent of patients with insulinomas will develop hypoglycemic symptoms within 24 hours and 100% within 48 hours (4,5).

Once a biochemical diagnosis of an insulinoma is established, localization procedures are performed. Due to their small size (82% <2 cm, 47% <1 cm), insulinomas are difficult to localize (1). Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are widely available and are noninvasive localizing studies. However, their accuracy for localizing tumors is poor (positive in <50% of cases) (6). Endoscopic US is positive in 70-95% of cases but often misses lesions in the tail of the pancreas, and is operator dependent (7).

Selective angiography can detect lesions in approximately 60% of patients and intra-arterial calcium stimulation with hepatic venous sampling for insulin levels localizes >80% of insulinomas, but it is invasive, costly, requires an experienced interventional radiologist, and only regionalizes the tumor (6,8).

Even when localizing studies are negative, all patients should undergo surgical exploration, with intraoperative US of the pancreas and manual palpation. Positron emitting radiopharmaceuticals for somatostatin receptor (SSTR) imaging, DOTA analogs, have been developed and show promising results, with high accuracy in detecting primary, recurrent, and metastatic tumors as compared to anatomic imaging, traditional radiopharmaceuticals, and endoscopy for gastrointestinal and pancreatic neuroendocrine tumors (NETs). These radioligands, which include ⁶⁸Gallium-DOTATATE, ⁶⁸Gallium-DOTATOC, and ⁶⁸Gallium-DOTANOC, have a high affinity to SSTR, especially to SSTR2. A comparison of this new SSTR imaging in a meta-analysis study suggested that ⁶⁸Gallium-DOTATATE was most accurate for detecting NETs (9). Recently, several studies have demonstrated that ⁶⁸Gallium-labeled somatostatin analog positron emission tomography (PET) when combined with CT has a higher sensitivity for detecting NETs than SSTR scintigraphy (10,11). In this report, we describe one patient in whom ⁶⁸Gallium PET/CT using the analogue DOTATATE localized a solitary, benign insulinoma with correlative immunohistochemical analysis.

Methods

Patients with a diagnosis of insulinoma at the National Institutes of Health (NIH) have noninvasive localization studies including transabdominal US, pancreatic protocol CT, and MRI. Arterial calcium stimulation with hepatic vein catheterization is also performed, which uses intravenous calcium as a secretagogue for the release of insulin from the islet cell tumors. The gastroduodenal, proper hepatic, superior mesenteric artery (SMA) and splenic arteries are selectively catheterized with calcium gluconate bolused into the selected artery. Blood samples from the right and left hepatic veins are obtained before and 20, 40, and 60 s after injection. A ≥ 2 -fold increase in insulin concentration from baseline localizes the insulinoma within the anatomic region perfused by the injected artery. A response after calcium infusion into the gastroduodenal or SMA localizes the lesion to the head and neck, whereas a response after

splenic artery injection localizes the lesion to the body and tail of the pancreas. A response following a hepatic artery injection suggests the presence of liver metastases (6,12).

⁶⁸Gallium-DOTATATE PET/CT is considered investigational and is not approved for routine use to localize NETs in the United States; therefore the current study was performed under a research protocol approved by the NIH Review Board and (NCT01967537). Through an antecubital vein, 5 mCi of ⁶⁸Ga-DOTATATE is administered. After 60 minutes, the patient is positioned in a PET/CT scanner and images from the upper thighs to the base of the skull are obtained. A non-contrast, non-diagnostic CT is used for attenuation and anatomic localization. Maximum standardized uptake values (SUV) are measured based on patient total body weight. An ¹¹¹In-pentetreotide SPECT/CT with imaging at 4 h and at 24 h following intravenous administration of 6 mCi (222 MBq) of ¹¹¹In-pentetreotide was performed.

For immunohistochemistry, primary antibody for SSTR2 [(UMB1) ab134152, Abcam, Cambridge, MA] and SSTR5 [(UMB4) ab109495, Abcam] was used at 1:60 dilution.

Case

A 40-year-old man with a longstanding history of seizures associated with hypoglycemia was referred to our institution. He had no significant past medical history. Physical examination was normal. The 48-hour supervised fast was stopped at 6 hours for neuroglycopenic symptoms with a blood glucose level of 33 mg/dL (reference range, 60-100 mg/dL). Symptoms resolved with administration of dextrose. The corresponding insulin was 12.9 mcU/mL (reference range, 2.6-24.9 mcU/mL), proinsulin was 130 pmol/L [point of discrimination ≥ 22 pmol/L (4)], C-peptide was 2.6 ng/mL (reference range, 1.1-5 ng/mL), and sulfonylurea screening was negative. His calcium level was normal at 2.35 mmol/L (reference range, 2.05-2.5 mmol/L) and his family history was negative for primary hyperparathyroidism or NETs.

An endoscopic US of the pancreas performed at another institution did not show any lesions. CT scan and MRI of the pancreas revealed a 2 cm lobulated lesion on the anterior aspect of the distal body (*Figure 1*). An arteriogram with selective arterial calcium stimulation and venous sampling, showed an arterial blush in the anterior aspect of the pancreatic body and increased insulin level with calcium-stimulation in the mid splenic at 20 s (*Figure 1E,F*). A ⁶⁸Gallium-DOTATATE PET/CT scan showed uptake in

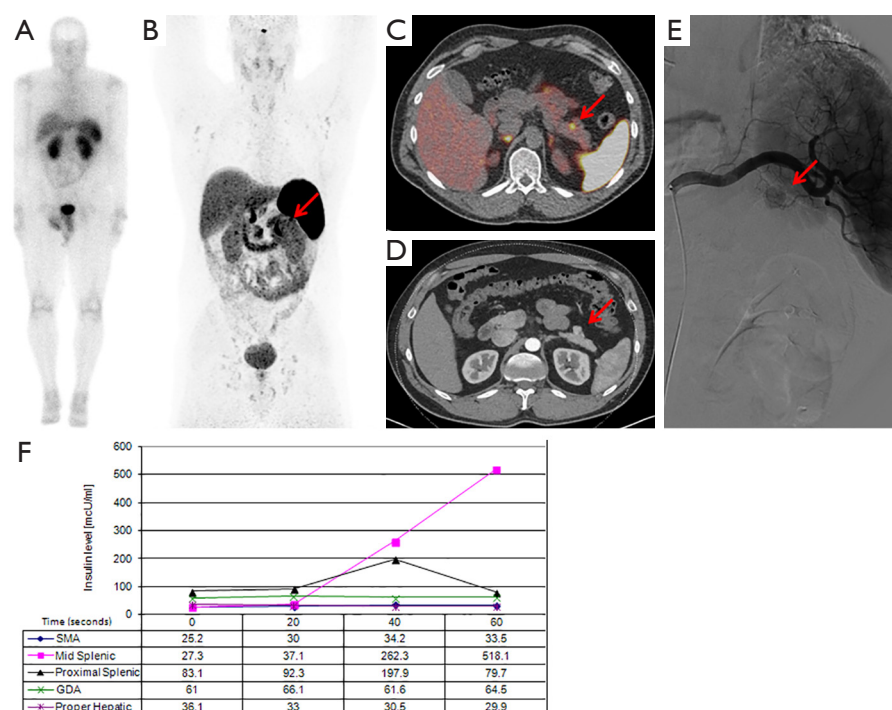


Figure 1 Multimodal imaging studies in a 40-year-old man with an insulinoma in the distal body of the pancreas. (A) $^{111}\text{Indium}$ -pentetreotide scan showing no uptake in the pancreas; (B,C) $^{68}\text{Gallium}$ -DOTATATE PET/CT showing a pancreatic tail mass (arrows) with a SUV of 18.5. Note there is normal physiologic uptake of $^{68}\text{Gallium}$ -DOTATATE in the spleen and adrenal gland; (D) arterial phase CT scan showing a superficial pancreatic mass with enhancement (arrow); (E) selective angiography of the splenic artery suggests a blush in the pancreatic body (arrow); (F) arterial calcium stimulation with venous sampling from the left hepatic vein showing increase insulin level at 20 s with stimulation in the mid-splenic artery. CT, computed tomography; PET, positron emission tomography; SUV, standard uptake value.

the anterior aspect of the distal body of the pancreas (*Figure 1B,C*). $^{111}\text{Indium}$ -pentetreotide scan and abdominal US were negative (*Figure 1A*).

The patient underwent a laparoscopic exploration and intraoperative US of the pancreas which showed a solitary, hypoechoic, vascular tumor on the anterior surface of the distal body of the pancreas. The tumor was enucleated. Pathology showed a 2.1 cm \times 1.6 cm \times 1.5 cm low grade (proliferative index Ki-67 staining $<2\%$), well-differentiated pancreatic NET that was positive for insulin, SSTR2 and SSTR5 expression (*Figure 2*). The patient remains euglycemic and free of symptoms 3.5 months after his operation.

Discussion

We report a case of benign, sporadic insulinoma that was detected for the first time using the radiotracer $^{68}\text{Gallium}$ -DOTATATE. In the United States, the use of $^{68}\text{Gallium}$ -

DOTATATE PET/CT is considered investigational and is not approved for routine use to localize NETs. The patient was evaluated on a prospective clinical protocol comparing the accuracy of anatomic imaging (CT), $^{111}\text{Indium}$ -pentetreotide scan and $^{68}\text{Gallium}$ -DOTATATE PET/CT. As shown in *Figure 1*, $^{68}\text{Gallium}$ -DOTATATE PET/CT provides anatomic information on the exact location of the lesion that shows DOTATATE avidity, with an SUV of 18.5.

The management of insulinomas is challenging and requires a multidisciplinary approach for diagnosis and localization. Although most insulinomas are <2 cm, our patient had a relatively large tumor (2.1 cm) which was detected by anatomic imaging. It has been previously reported that $^{68}\text{Gallium}$ -DOTATATE PET/CT can detect NETs as small as 6 mm (10,13). The sensitivity of $^{111}\text{Indium}$ -pentetreotide scintigraphy to detect insulinomas is lower than for most gastrointestinal NETs, sensitivity of 20-60% (14-16), even though insulinomas are reported to express SSTR2 and 5 (17). These receptors have been

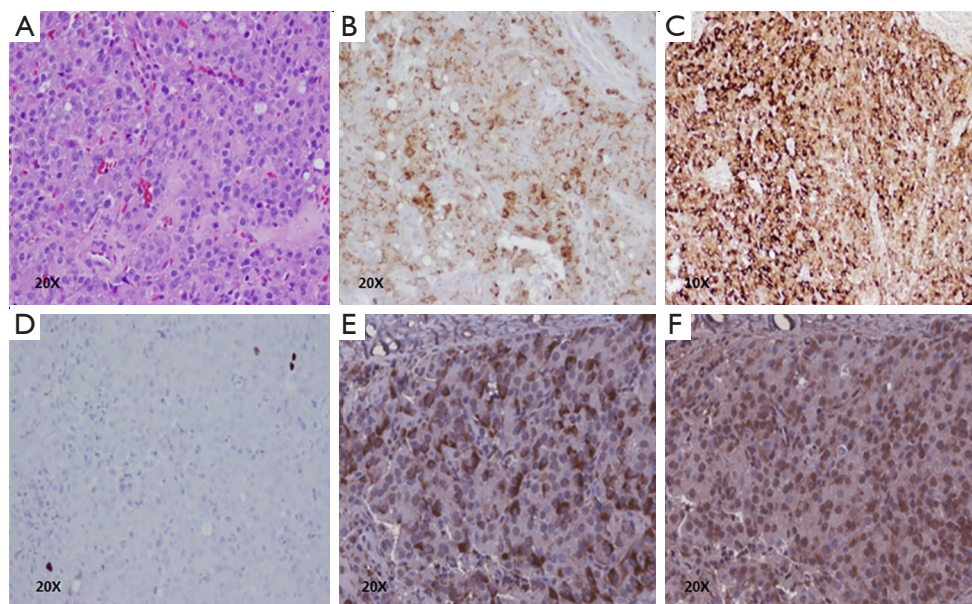


Figure 2 Histopathology of insulinoma. Immunohistochemistry studies, with H&E stained sections showing a neuroendocrine tumor, grade 1 (A). Tumor cells stain for chromogranin A (B), insulin (C) and low proliferative index Ki-67 staining (<2%) (D). Tumor cells stain for SSTR2 on cell membrane and cytoplasm (E) and for SSTR5 in the cytoplasm (F). H&E, Hematoxylin and Eosin; SSTR, somatostatin receptor.

successfully targeted in gastrointestinal and pancreatic NETs with ⁶⁸Gallium-DOTATATE, at a comparable diagnostic accuracy as other tracers such as DOTANOC (11,18). These findings suggest that ⁶⁸Gallium-DOTATATE has high affinity for SSTR2 and SSTR5 and thus when positive, are specific for NETs in the pancreas as observed in our patient. Another recently described radioligand to detect insulinomas is ¹¹¹In-labelled exendin-4 which displays a high sensitivity for insulinomas because it targets the glucagon-like peptide 1 receptor, which is highly expressed in insulinomas (19-21).

Although the diagnosis of insulinoma is a biochemical diagnosis, localization of these tumors before surgical treatment can facilitate the type of surgical procedure used and improves the likelihood of successful surgical treatment. At our institution, patients undergo multimodal localizing studies. All of these localizing studies should be considered complementary in the management of patients with insulinoma.

In conclusion, ⁶⁸Gallium-DOTATATE PET/CT could be a helpful adjunct localizing study to detect insulinomas, especially when other localizing studies such as endoscopic US and calcium stimulation are unrevealing. A larger study is needed to fully assess the accuracy of ⁶⁸Gallium-

DOTATATE PET/CT in patients with insulinoma as compared to current localizing studies used in clinical practice.

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