

Received: 2020.02.07

Accepted: 2020.04.17

Available online: 2020.05.18

Published: 2020.06.14

Changing Insulinoma Management Due to Incidentally Discovered Metastasis: A Case Report

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Riya Madan**
D 2 **Tetyana Mettler**
D 3 **Jerry Froelich**
AEF 4 **Lisa S. Chow**

1 University of Minnesota Medical School, Minneapolis, MN, U.S.A.

2 Department of Laboratory Medicine and Pathology, University of Minnesota Medical Center, Minneapolis, MN, U.S.A.

3 Department of Radiology, University of Minnesota Medical Center, Minneapolis, MN, U.S.A.

4 Department of Diabetes, Endocrinology and Metabolism, University of Minnesota Medical Center, Minneapolis, MN, U.S.A.

Corresponding Author: Lisa S. Chow, e-mail: chow0007@umn.edu

Conflict of interest: None declared

Patient: Female, 46-year-old
Final Diagnosis: Metastatic insulinoma
Symptoms: Altered mental status • anxiety • hypoglycemia • unsteadiness
Medication: —
Clinical Procedure: EUS-guided ablation • EUS-guided FNA
Specialty: Endocrinology and Metabolic

Objective: Rare disease

Background: Hypoglycemia is rare in individuals without drug-treated diabetes mellitus. In a seemingly well individual, the differential diagnosis of hypoglycemia narrows to 2 major categories: 1) accidental, surreptitious, or intentional hypoglycemia, or 2) endogenous hyperinsulinism (EHH). Insulinomas are the most common cause of EHH. Localization of insulinomas can be challenging, as most tumors are less than 2 cm in size and may be present in any part of the pancreas. In fact, almost 30% of neuroendocrine tumors (NET) cannot be located preoperatively by traditional imaging techniques such as computerized tomography (CT) or magnetic resonance imaging (MRI).

Case Report: This report describes a case of metastatic insulinoma in a patient with a complex medical history. CT with contrast of the abdomen identified 1 lesion located in the pancreas body. Endoscopic ultrasound (EUS) identified an additional 3 to 4 hypoechoic lesions in the pancreatic neck and body. 68-Gallium Dotatate scanning identified 3 distinct lesions within the pancreas and a right posterior rib sclerotic lesion.

Conclusions: Reliance upon traditional imaging techniques (CT/MRI) for tumor localization would not have identified the multifocal pancreatic lesions and the metastatic bone lesion. Accurate identification of multifocal, metastatic insulinomas requires multiple imaging modalities, including first-line non-invasive imaging (CT or MRI) followed by second-line imaging (EUS or nuclear imaging).

MeSH Keywords: Endoscopic Ultrasound-Guided Fine Needle Aspiration • Insulinoma • Magnetic Resonance Imaging • Neuroendocrine Tumors • Nuclear Medicine • Tomography, X-Ray Computed

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/923356>
 2125

 1

 5

 15


Background

Hypoglycemia is rare in individuals without drug-treated diabetes mellitus [1], but many adults, particularly women, report symptoms attributed to reactive hypoglycemia, a postprandial hypoglycemic state occurring within 2–5 h after eating [2]. In the absence of bariatric surgery, there are multiple causes of postprandial hypoglycemia, including insulinoma [3,4]. As insulinomas have the potential to be definitively treated by surgery [4], insulinoma identification is important.

To do so, it is important to consider satisfying Whipple's triad (hypoglycemia symptoms, documentation of hypoglycemia on testing, and symptom resolution with glucose administration) before pursuing a hypoglycemia workup. Patients who satisfy Whipple's triad and are otherwise "seemingly well" typically have hypoglycemia arising from either: 1) accidental, surreptitious, or intentional hypoglycemia or 2) endogenous hyperinsulinism (EHH) [1]. Insulinomas, a type of islet cell tumor, are the most common cause of EHH [5], although insulinomas remain quite rare, with an incidence of 1 in 250 000 patient-years [1]. Patients with insulinomas demonstrate hypoglycemia exclusively in the fasting state (73%), exclusively in the postprandial state (6%), and in fasting and postprandial state (21%) [4]. Less than 10% of patients with insulinomas have multiple tumors. Here, we present a case of a patient with a metastatic insulinoma and compare the various imaging modalities needed to identify metastatic insulinoma tumors.

Case Report

A 46-year-old woman presented to the Emergency Department (ED) via ambulance after coworkers noticed her odd behavior at work. At the workplace, the paramedics used a glucose meter and reported her capillary fingerstick glucose at 29 mg/dL. She was given a ½ ampule of D50 and her glucose level increased to 111 mg/dL. When she arrived at the ED 30 min later, her glucose level had dropped to 32 mg/dL. The ED evaluation was significant for a urinary tract infection (UTI). Therefore, her hypoglycemia was attributed to the UTI and she was discharged home with Bactrim and a home glucometer. Two days later, she returned to the ED with self-reported anxiety. Her fasting glucose values using her home glucometer were 33 mg/dL, 59 mg/dL, 55 mg/dL, and 70 mg/dL. Upon arrival to the ED, her capillary fingerstick glucose was 79 mg/dL. Her medications included levothyroxine, lisinopril, olanzapine, citalopram, vitamin D3, and fish oil. Her medical history was significant for legal blindness, hypothyroidism, and multiple behavior and psychiatric issues which prevented her from living independently from her family. Her family history was significant for nephrolithiasis, "thyroid tumor" of unknown etiology in the patient's mother, and episodes of unevaluated

Table 1. Laboratory findings supportive of endogenous hyperinsulinemia.

Finding	Pattern in insulinoma	Pattern in patient
Symptoms, signs, or both	Yes	Yes
Glucose (mg/dl)	<55	57
Insulin (μU/ml)	≥3	23.2
C-peptide (nmol/liter)	≥0.2	1.72
Proinsulin (pmol/liter)	≥5	82.3
β-Hydroxybutyrate	≤2.7	Not obtained (lab error)
Glucose increase after glucagon (mg/dl)	>25	82
Circulating oral hypoglycemic agent	No	No
Antibody to insulin	Neg	Neg

hypoglycemia in the patient's sister, and negative for diabetes in the immediate family. She is a never smoker and had no alcohol or substance use. During her second ED evaluation, she indicated that she noticed having spells of odd behavior with associated unsteadiness, which had been progressive over the last few months. She reported that these symptoms improved upon the ingestion of "sugar water." The patient was extensively interviewed regarding her medical history and her proximity to diabetes medications/other individuals with diabetes. A physical exam was unremarkable.

The medical team felt that the patient's presentation met the criteria for Whipple's triad [1] with documented hypoglycemia. As she was not acutely ill and had no history of diabetes mellitus, she fell into the category of a "seemingly well patient", presenting with hypoglycemia either due to accidental, surreptitious, or malicious hypoglycemia or endogenous hyperinsulinism.

Evaluation

The patient's initial presentation strongly supported Whipple's triad, as the presentation was characterized by neuroglycopenic symptoms, evidence of hypoglycemia (glucose <60 mg/dL measured on home blood glucose monitoring), and resolution of her neuroglycopenic symptoms with glucose treatment. By the time she was evaluated by the Endocrinology consult service, she was already receiving treatment for her hypoglycemia, which included being placed on a hypoglycemia protocol (12.5 g IV D50 injection for blood glucose less than 50 mg/dL in an alert patient). Glucose, C-peptide, and proinsulin levels were obtained when the patient had symptoms of hypoglycemia (Table 1). Although these results (Table 1) do not strictly

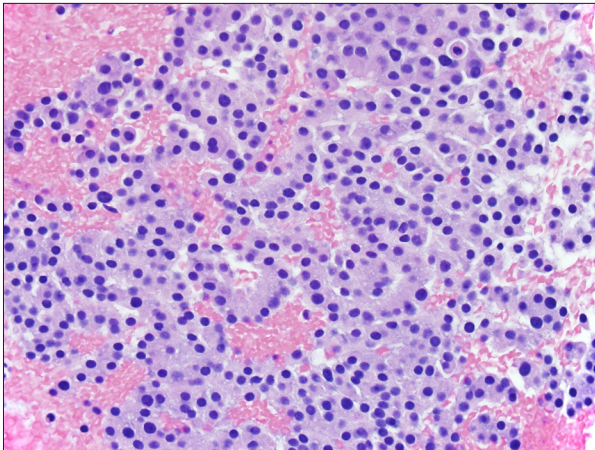


Figure 1. Histopathology: Cell block preparation shows pancreatic neuroendocrine tumor composed of cells with uniform round nuclei (hematoxylin-eosin (H&E) stain, magnification 40×).

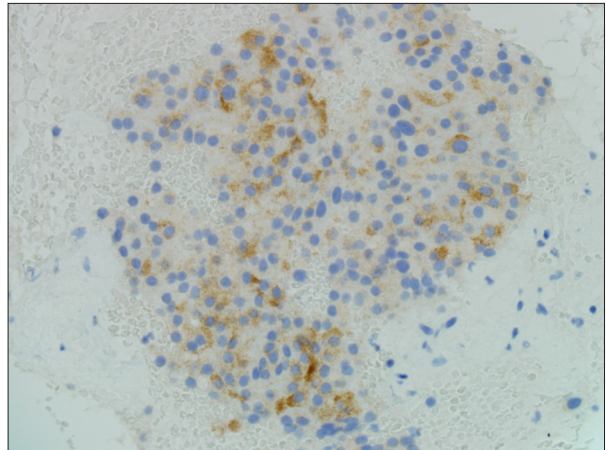


Figure 2. Histopathology: Tumor cells show cytoplasmic reactivity for insulin immunostain (magnification 40×).

meet the definition of endogenous hypoglycemia (plasma glucose <55 mg/dL if Whipple's triad was previously documented), the results are supportive of hyperinsulinemic hypoglycemia [1].

In addition, her CT scan at the time of admission evaluation identified a pancreatic tumor highly suspicious for insulinoma. Because she satisfied Whipple's triad and her CT imaging was suspicious for insulinoma, the 72-h fast was not performed.

Computed tomography of the abdomen/pelvis with IV contrast identified a 1.5×0.9 cm enhancing lesion in the body of the pancreas. An invasive endoscopic ultrasound (EUS) was conducted to more accurately localize this lesion, and identified an additional 3 to 4 hypoechoic lesions in the pancreatic neck and body. EUS-guided fine-needle biopsy in the pancreatic body and neck was highly suspicious for a neuroendocrine tumor (NET) (Figure 1). Tumor cells were positive for synaptophysin, chromogranin, and CD56, which are all markers for NETs. Ki-67 showed low proliferation index, estimated as <3%. The tumor cells were weakly positive for insulin stain (Figure 2). A 68-Gallium Dotatate scan was conducted, which showed 3 distinctive tumor sites within the pancreas (Figures 3, 4), a right posterior rib sclerotic lesion (Figure 5), and small bilateral pleural effusions and extensive bilateral posterior lower lobe atelectasis/consolidation.

Given the multicentric nature of the lesions, MEN-1 syndrome was considered. However, as multiple measurements of her calcium level had produced normal results, the Endocrinology team felt that the possibility of primary hyperparathyroidism was extremely low; therefore, the MEN-1 mutation was not measured.

Treatment plan

The surgical team felt that the patient was not a good surgical candidate due to her multiple comorbidities. These included the inability to live independently due to behavior and psychiatric issues, legal blindness, EUS-identified multifocal insulinoma, and potential bone metastasis. Thus, the patient was started on diazoxide (88 mg/ml TID) to control her hypoglycemia. For treatment of the noted metastatic insulinoma, we offered EUS-based ablation. EUS-guided ablation of the largest lesion was conducted; however, remaining lesions were left alone. The next day, after the ethanol ablation, the patient was discharged on the diazoxide program (88 mg/ml TID). The patient's family was contacted by phone several times (at 2 weeks, 4 weeks) after discharge. Per family report, the patient did not take any more diazoxide after her prescription ran out, roughly 10 days after discharge. When contacted 4 weeks after discharge, the patient's family reported that the patient had no further episodes of hypoglycemia with neuroglycopenic symptoms.

Discussion

The teaching point of this case is that multiple imaging modalities are required for the detection of metastatic insulinoma tumors and that identification of metastatic insulinomas will alter management. In this case, CT imaging of the patient was positive for 1 lesion in the pancreatic body but was unable to localize the additional lesions present in the pancreatic neck that were identified by EUS. In fact, almost 30% of NETs are not located preoperatively by traditional imaging techniques such as CT, US, or MRI [6], as most insulinoma tumors are solitary and < 2 cm in size. As complete surgical resection of tumors is the only curative treatment, inaccurate localization of tumors can result in persistence of symptoms and need for

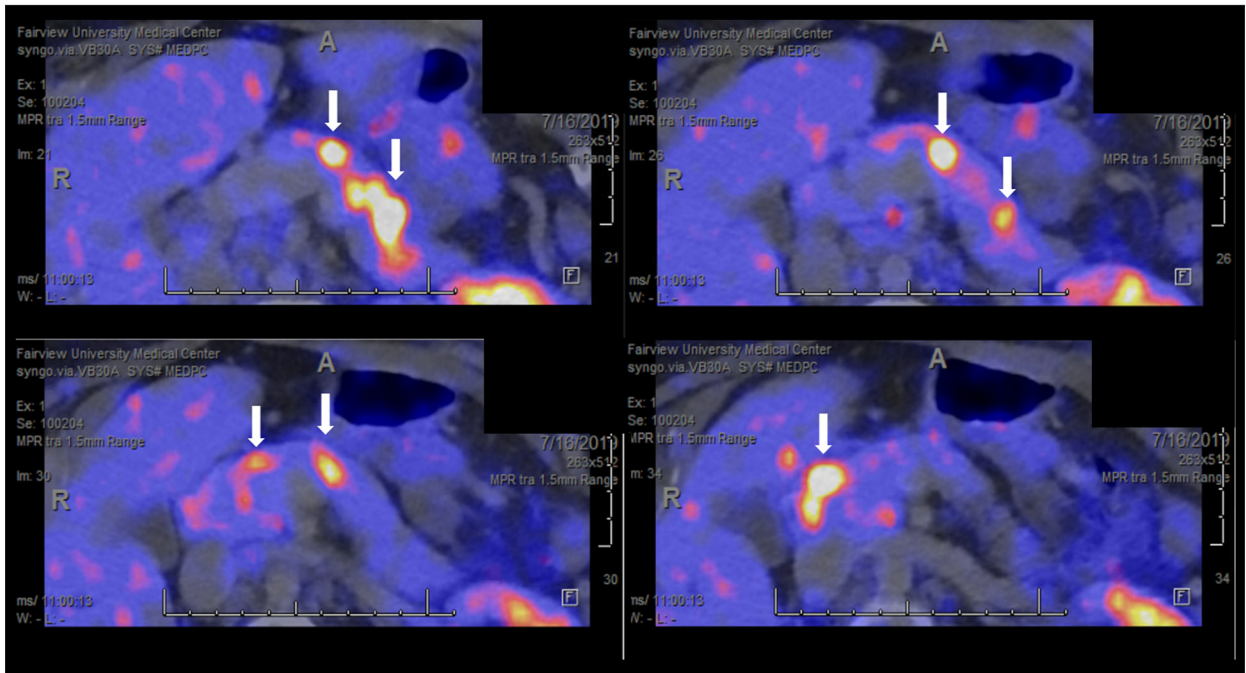


Figure 3. Ga68Dotatate PET demonstrating 3 foci of intense uptake in the body and tail of the pancreas, consistent with a multifocal insulinoma (arrows). Images arranged from caudal to cranial.

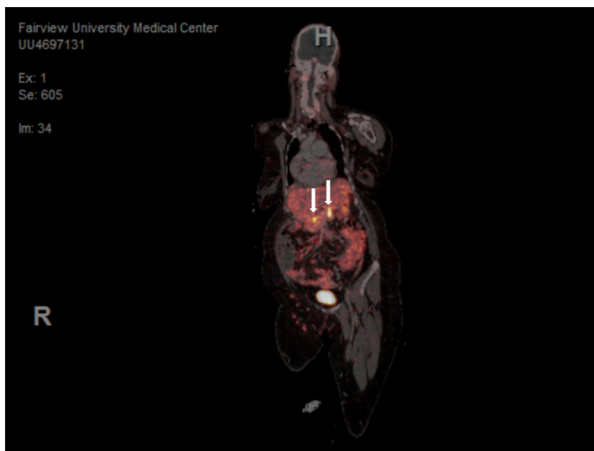


Figure 4. Ga68Dotatate PET demonstrating foci of intense uptake in the body and tail of the pancreas, consistent with a multifocal insulinoma (arrows).

re-resection. Thus, multiple imaging modalities are required for detecting metastatic insulinoma tumors.

CT/MRI

First-line imaging for insulinoma localization is by non-invasive modalities such as CT or MRI. Dual-phase CT scans have >90% sensitivity for detecting insulinomas [7]. CT scans are simple to perform, relatively cheap, and can detect liver metastases. As we observed in this case, CT was unable to identify smaller tumors and tumors that extend into extra-pancreatic

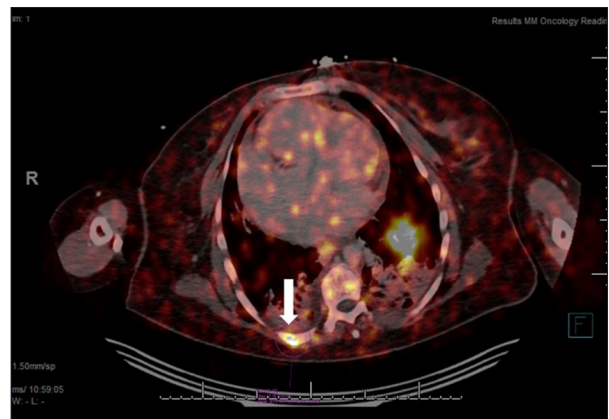


Figure 5. Ga68Dotatate PET demonstrating focus of intense uptake in the right posterior rib (arrow).

tissue, similar to previous observations [8]. MRI is superior to CT in the ability to detect extra-pancreatic extension of tumors. Some studies have shown that diffusion-weighted MRI can detect tumors that CT scans have missed, with detection rates of 75% compared to 64%, respectively [9]. However, the sensitivity of detecting insulinoma with MRI is lower and more variable than that of CT, ranging between 40% and 90% [10]. Additionally, MRI is more expensive than CT. Other non-invasive modalities include transabdominal sonography (USG) and contrast-enhanced sonography (CEUS), and these imaging techniques are also advantageous due to their general availability and low cost. However, the average sensitivity of USG in localizing lesions is less than 70% [11]. Barriers

to detection specific to USG include localization difficulty due to bowel gas, operator dependency, and increased abdominal fat, which is commonly observed in insulinoma patients. Consequently, USG remains a rarely used non-invasive insulinoma imaging modality [8].

EUS

Invasive imaging is often the next step needed for accurate localization of the multiple tumors that may be present in an insulinoma patient's disease pathology. Endoscopic ultrasound (EUS) is one such imaging method that was used in the diagnosis of this patient. The sensitivity and accuracy of diagnosing insulinomas in patients with hypoglycemia is significantly higher in EUS than CT, at 100% and 60% vs. 95.4% and 68%, respectively [6]. EUS allows identification of lesions as small as 4 mm, with the additional advantage of tissue sampling. However, CT scans have distinct advantages in identifying distant metastases; therefore, these 2 imaging modalities are best used complementarily [6]. The additional benefit provided by EUS is its ability to provide local therapy for insulinoma via EUS-guided alcohol injection of the noted lesions in patients who are not surgical candidates [8].

Nuclear medicine imaging

Nuclear medicine imaging can also be valuable in insulinoma imaging. The radiopharmaceuticals approved by the FDA include the Octreoscan (1994), 18F-fluorodeoxyglucose (18FFDG) PET/CT (2004), and, most recently, the 68-Gallium Dotatate scan (2016), which was used for imaging in this patient [8]. The 68-Gallium Dotatate scan is an imaging modality that targets somatostatin receptors (SSTR) expressed on NETs. It has a high affinity to SSTR 2, which is present in up to 80% of insulinoma cases [12]. An advantage of the 68-Gallium Dotatate scan is its ability to exclude the presence of additional pancreatic NETs not detected by anatomic imaging in syndromes like MEN1 [12]. A large prospective study evaluated the clinical utility of 68-Gallium Dotatate scans for management of NETs. In 131 patients, of at least 18 years of age, and with biochemical or radiologic suspicion and/or known diagnosis of NET, the 68-Gallium Dotatate scan was found to have a higher sensitivity for detecting NETs compared to conventional anatomic imaging (i.e., CT/MRI) and to 111-In pentetreotide SPECT/CT imaging [13]. The 68-Gallium Dotatate scan detected significantly more tumors than anatomic imaging and 111-In pentetreotide SPECT/CT (95%, 45%, and 30.9% respectively). The 68-Gallium Dotatate scan also had the highest true-positive rate compared to 111-In pentetreotide and anatomic imaging (72%, 22%, and 39%, respectively). Adding the 68-Gallium Dotatate scan significantly altered clinical management of 33% of patients by increasing clinical surveillance, surgical intervention, and targeted chemotherapy of tumors [13].

Since many insulinomas have high concentrations of glucagon-like peptide-1 (GLP-1) receptors [14], GLP-1 radioligands that bind to the GLP-1 receptor have been developed to facilitate insulinoma localization. Recently, a small prospective study enrolled 8 patients with biochemically-proven insulinoma and with negative or inconclusive conventional imaging (CT, MRI, EUS, and somatostatin receptor scintigraphy). Whole-body single-photon emission tomography/computed tomography (SPECT/CT) imaging was performed 4 h after injection of a Tc-99m-labelled GLP-1 receptor agonist. Surgical resection was performed based on imaging findings. In all patients, surgical pathology confirmed the insulinoma diagnosis. None of the patients had any further recurrence of their hypoglycemia during post-surgical follow-up (range 1–75 months, median 24.5 months) [15].

We acknowledge several limitations of this case report. First, the evaluation for hypoglycemia did not include the 72-h fast and her laboratory evaluation did not meet the classic guidelines for an insulinoma [1]. Given the patient's concurrent behavior/psychiatric issues which prevented her from being able to fast for 72 h, the presence of ongoing treatment of her hypoglycemia, her initial presentation fulfilling the criteria for Whipple's triad, and abdominal imaging suspicious for an insulinoma, we felt that there was sufficient clinical evidence to support more definitive diagnosis by further imaging/EUS than meeting the classic laboratory evidence for an insulinoma. Another limitation is that the follow-up was by self-report, as the patient did not return to our institution for formal reassessment. Despite these limitations, the teaching point remains that additional imaging options should be considered prior to definitive management, as identification of a multifocal or metastatic insulinoma will alter management.

Conclusions

Insulinomas are pancreatic lesions that are the primary cause of most cases of endogenous hyperinsulinism. Localization of insulinomas can be challenging, as most tumors are often less than 2 cm and may be present in any part of the pancreas. Identification of multifocal, metastatic insulinomas require multiple imaging modalities, including first-line non-invasive imaging (CT or MRI) followed by second-line imaging such as EUS and nuclear imaging. As demonstrated in this case, identification of multifocal, metastatic insulinoma directly altered clinical management of the patient.

Conflict of interest

None.

References:

1. Cryer PE, Axelrod L, Grossman AB et al: Evaluation and management of adult hypoglycemic disorders: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*, 2009; 94(3): 709–28
2. Simpson EJ, Holdsworth M, Macdonald IA: Prevalence of self-reported symptoms attributed to hypoglycaemia within a general female population of the UK. *J Psychosom Res*, 2006; 60(4): 403–6
3. Shah P, Rahman SA, Demirbilek H et al: Hyperinsulinaemic hypoglycaemia in children and adults. *Lancet Diabetes Endocrinol*, 2017; 5(9): 729–42
4. Placzkowski KA, Vella A, Thompson GB et al: Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *J Clin Endocrinol Metab*, 2009; 94(4): 1069–73
5. Woo C-Y, Jeong JY, Jang JE et al: Clinical features and causes of endogenous hyperinsulinemic hypoglycemia in Korea. *Diabetes Metab J*, 2015; 39(2): 126–31
6. Varas Lorenzo MJ, Miquel Collell JM, Maluenda Colomer MD et al: Preoperative detection of gastrointestinal neuroendocrine tumors using endoscopic ultrasonography. *Rev Esp Enferm Dig*, 2006; 98(11): 828–36
7. Gouya H, Vignaux O, Augui J et al: CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. *Am J Roentgenol*, 2003; 181(4): 987–92
8. Rayamajhi SJ, Lee J, Mittal BR et al: Cross sectional and nuclear medicine imaging of pancreatic insulinomas. *Abdom Radiol (NY)*, 2017; 42(2): 531–43
9. Druce MR, Muthuppalaniappan VM, O'Leary B et al: Diagnosis and localisation of insulinoma: the value of modern magnetic resonance imaging in conjunction with calcium stimulation catheterization. *Eur J Endocrinol*, 2010; 162(5): 971–78
10. McAuley G, Delaney H, Colville J et al: Multimodality preoperative imaging of pancreatic insulinomas. *Clin Radiol*, 2005; 60(10): 1039–50
11. Mehrabi A, Fischer L, Hafezi M et al: A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas*, 2014; 43(5): 675–86
12. Nockel P, Babic B, Millo C et al: Localization of insulinoma using 68Ga-DOTATATE PET/CT scan. *J Clin Endocrinol Metab*, 2017; 102(1): 195–99
13. Sadowski SM, Neychev V, Millo C et al: Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol*, 2016; 34(6): 588–96
14. Reubi JC, Waser B: Concomitant expression of several peptide receptors in neuroendocrine tumours: Molecular basis for *in vivo* multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging*, 2003; 30(5): 781–93
15. Senica K, Tomazic A, Skvarca A et al: Superior diagnostic performance of the GLP-1 receptor agonist [Lys(40)(Ahx)HYNIC-[(99m)Tc]/EDDA)NH₂]-Exendin-4 over conventional imaging modalities for localization of insulinoma. *Mol Imaging Biol*, 2020; 22(1): 165–72