ACG CASE REPORTS JOURNAL

CASE REPORT | PANCREAS

Malignant Insulinoma Arising From Nonfunctioning Pancreatic Neuroendocrine Tumor

Ritodhi Chatterjee, MD[1], Basim Ali, MD[1], Son H. Nguyen, DO[2], Rui Chen, MD[2], and Yvonne H. Sada, MD[3]

[1]*Department of Internal Medicine, Baylor College of Medicine, Houston, TX*
[2]*Section of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, Baylor College of Medicine, Houston, TX*
[3]*Section of Hematology and Oncology, Department of Internal Medicine, Baylor College of Medicine, Houston, TX*

ABSTRACT

Pancreatic neuroendocrine tumors are rare neoplasms characterized into nonfunctioning (NF-PNET) and functioning (F-PNET) subtypes. F-PNETs typically involve overt symptoms related to excessive hormone secretion but may rarely present first as NF-PNETs with delayed transformation. We present a patient with known NF-PNET with liver metastases who developed hypoglycemia 2 years after initial diagnosis due to malignant insulinoma. Hypoglycemia was refractory to continuous dextrose but improved temporarily after diazoxide and hepatic artery embolization. Malignant insulinomas are usually metastatic at presentation and portend poor prognosis. Hypoglycemia may be medically managed with steroids, somatostatin analogues, and diazoxide, along with therapies to reduce tumor burden.

KEYWORDS: pancreatic neuroendocrine tumor; insulinoma; hepatic artery embolization; diazoxide; liver metastases

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms comprising <3% of all pancreatic malignancies, with an annual incidence of ≤1 case per 100,000 individuals.[1] They are classified into nonfunctioning (NF-PNET) and functioning (F-PNET) subtypes. A small body of literature reports transformation of NF-PNETs into hormonally active phenotypes later in the disease course. Insulinomas are the most common F-PNET and carry high morbidity and mortality because of associated hypoglycemia.[2] We present a patient with biopsy-proven NF-PNET found to have malignant insulinoma 2 years after initial diagnosis.

CASE REPORT

A 39-year-old man with treatment-refractory nonfunctioning PNET (NF-PNET) and distant metastases presented with recurrent hypoglycemic symptoms.

Two years prior, a hepatic mass was discovered incidentally on abdominal ultrasound performed at the request of the patient because of recent diagnosis of gallstones in a family member. Computed tomography showed an ill-defined 4.2 × 3.8-cm mass of the pancreatic head with lymphadenopathy and a 1.9-cm lesion of the right hepatic lobe. Endoscopic ultrasound-guided fine-needle aspiration of a peripancreatic lymph node yielded pathologic confirmation of low-grade PNET (Ki-67 <1%). Liver biopsy demonstrated neuroendocrine metastasis with high-grade features (Ki-67 30%). Over 2 years, disease progressed on several lines of antineoplastic treatment, including (chronologically) octreotide, capecitabine/temozolomide, microwave ablation of liver lesions, everolimus, sunitinib, and cisplatin/etoposide. Pancreatic mass measured 7.8 × 7.7 × 7 cm with >40 liver metastases on imaging 2 months before presentation (Figure 1).

In the emergency department, the patient reported episodic fatigue, night sweats, palpitations, and hunger pangs for 3 weeks that resolved with carbohydrate intake, culminating in loss of consciousness. A fingerstick test in the ambulance showed serum glucose of 45 mg/dL. His medical history was notable for pancreatic insufficiency, non–insulin-dependent diabetes mellitus, and obesity (body

ACG Case Rep J 2023;10:e00954. doi:10.14309/crj.0000000000000954. Published online: January 27, 2023

Correspondence: Ritodhi Chatterjee, MD (Ritodhi.chatterjee@bcm.edu).

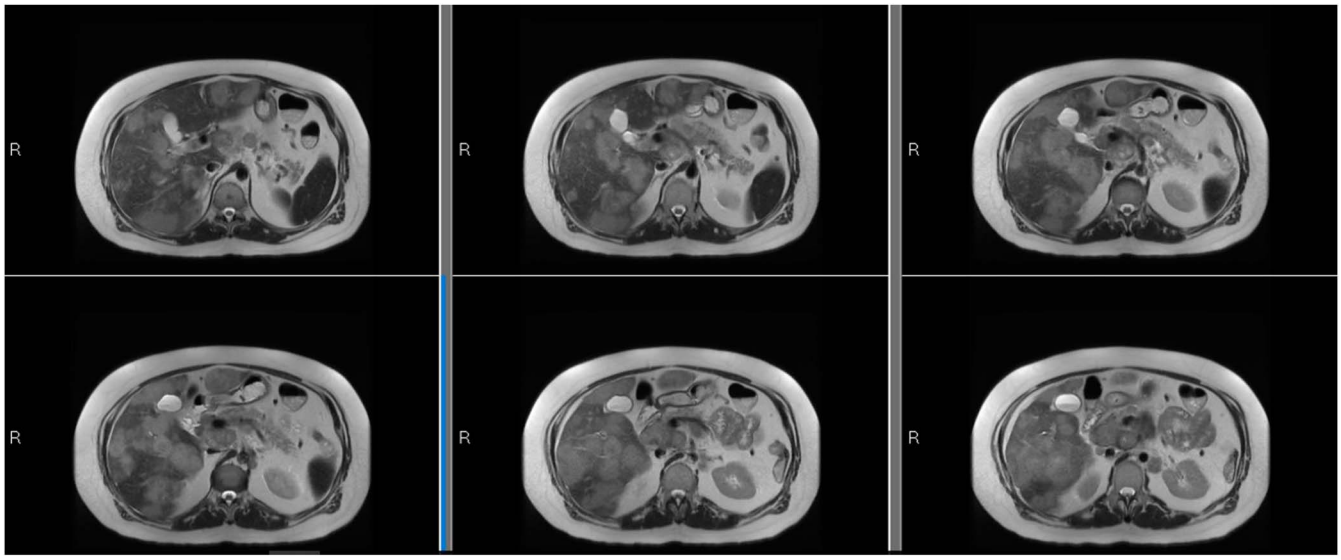

Figure 1. T2-weighted axial magnetic resonance images demonstrating greater than 40 diffuse hepatic metastases, the largest measuring 8.5 × 5.3 cm in segment 5/6 and 6.2 × 6.9 cm in the right hepatic dome. Porta hepatis nodal conglomerate measuring 3.9 cm is also noted.

mass index 37 kg/m^2). Vital signs were notable for sinus tachycardia of 125 beats per minute and temperature of 99.6°F. Physical examination revealed hepatomegaly. Initial laboratory studies were as follows with reference ranges: glucose 43 (65–110 mg/dL), hemoglobin 9.7 (12.0–18.0 g/dL), white blood cell count 1.7 (3.5–10.0 × 10^3 cells/μL), aspartate aminotransferase 49 (10–42 IU/L), alanine aminotransferase 18 (7–55 IU/L), and alkaline phosphatase 134 (38–127 IU/L). The last hemoglobin A1c was 7.3 (4.2%–5.8%) 6 months before presentation. Lactic acid and blood cultures were negative.

Despite intravenous fluids containing 10% dextrose (D10), the patient continued to have intermittent hypoglycemia. A hypoglycemic disorder was diagnosed through observation of Whipple's triad: low plasma glucose (35 mg/dL), symptoms of hypoglycemia (diaphoresis and weakness), and relief with glucose correction. The following laboratory abnormalities confirmed insulinoma: serum insulin 70.4 (2.6–24.9 μIU/mL), C-peptide 12.6 (1.1–4.4 ng/mL), and proinsulin 407.6 (0.0–10.0 pmol/L). Remaining hypoglycemia workup including cortisol, beta-hydroxybutyrate, growth hormone, growth hormone–releasing hormone, insulin autoantibody, and sulfonylurea screen was negative.

Recurrent hypoglycemia persisted after 2 weeks despite D10 infusion at 225 mL/hr, 60 mg of oral prednisone daily, lanreotide, and a trial of inpatient chemotherapy with FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan). By day 22, the patient was receiving concentrated 50% dextrose (D50) at 140 mL/hr through the central line, 200 mg of prednisone daily, with frequent pushes of additional D50.

Bland right hepatic artery embolization, injection of embolizing agents without delivery of chemotherapy, was performed on day 23 to reduce tumor burden, with a concurrent trial of antihypoglycemic agent diazoxide uptitrated to maximum daily dose of 900 mg. The patient developed mild tumor lysis syndrome managed with continued hydration and patiromer for hyperkalemia, but hypoglycemia completely resolved 3 days later (Figure 2). D50 infusion was discontinued, and steroids were weaned to physiologic levels. Diazoxide was reduced to 200 mg thrice daily at discharge.

Two months later, the patient was readmitted with congestive heart failure and anasarca, likely multifactorial in etiology from large-volume intravenous fluid administration during prior hospitalizations, decreased hepatic synthetic function from extensive liver metastasis, and newly decreased right ventricular systolic function on echocardiography, a well-reported adverse effect of diazoxide.[3] Hypoglycemia recurred off diazoxide, and the patient was again placed on intravenous dextrose. Weary of another prolonged hospitalization, he elected for hospice and died soon after requesting discontinuation of dextrose infusions.

DISCUSSION

Transformation of NF-PNETs into hormonally active functioning subtypes is a rare occurrence. This biological switch occurs in just 3.4%–6.8% of PNETs, and insulinomas are the most commonly reported phenotype, likely because of overt clinical symptoms.[4] Only 28 other cases of malignant insulinomas arising from prior NF-PNETs have been described previously (Table 1). The median age at presentation was 56.5 years (range: 31–74), and the median duration from initial NF-PNET diagnosis was 47 months (range: 4–240). Some patients presented with symptomatic hypoglycemia while actively undergoing treatment or with recurrent disease after complete resection of NF-PNET, sometimes years later. The phenotypic change often coincided with new or rapidly growing distant metastases. Heterogeneity of tumor differentiation in our

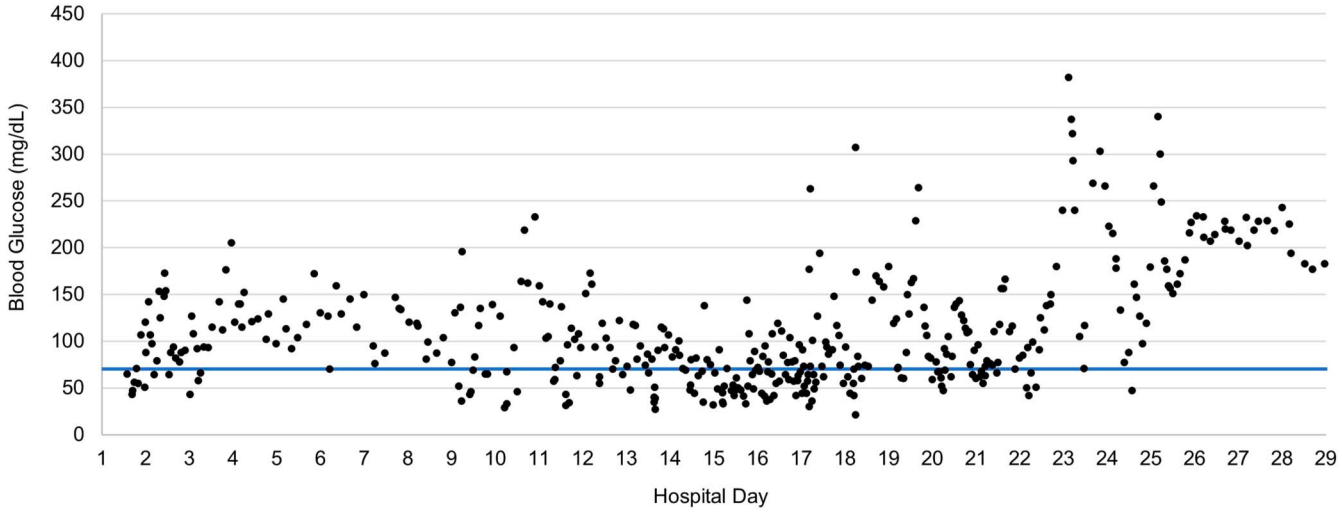

Figure 2. Scatter plot of inpatient blood glucose measurements. The blue line marks 70 mg/dL, the lower bound of normal at our institution. D10 infusion was initiated on day 1, D20 on day 16, and D50 on day 18. Diazoxide was initiated, and the patient underwent hepatic artery embolization on day 22. Dextrose supplementation was discontinued on day 25.

patient between lymph nodes and the liver may have foreshadowed transformation to F-PNET. Transformation portended poor prognosis, with only 5 of 28 (17.9%) patients remaining alive at report publication. The median survival was 12 months (range: 1–29).

Several mechanisms have been proposed for this late-onset gain of function. Mirroring functional plasticity of multipotent progenitor cells in the pituitary, pancreatic stem cells may differentiate into insulin-secreting tumor cells de novo on metastasis to the liver.[5] Studies have demonstrated the expression of hormones including insulin in NF-PNETs, and nearly all cases of transformation to malignant insulinoma were preceded by liver metastasis; these initially inactive neoplasms may thus harbor insulin-producing but clinically silent cells that potentiate in the milieu of the liver through an unknown pathophysiologic mechanism.[6–8] The receptor tyrosine kinase inhibitor sunitinib may be implicated, as in vitro studies have demonstrated its ability to trigger epigenetic changes in cancer cells, and tyrosine kinase inhibitors can cause hypoglycemia.[2,8] Sunitinib preceded symptoms in 8 of 28 cases (28.6%), although rarely as monotherapy; our patient received sunitinib 4 months before hospitalization. Recently, Yu et al have theorized that acquired functionality represents the natural history of malignant PNETs. Volume of insulin-secreting cells may gradually expand with increasing tumor bulk, that is, with liver metastasis, and eventually surpass the threshold necessary to trigger hypoglycemia.[9] Therefore, perhaps all malignant insulinomas start off as NF-PNETs until clinically unmasked.

Although surgery is curative for benign insulinomas, malignant tumors are often metastatic at diagnosis. Alcohol or radiofrequency ablation, selective bland tumor embolization, or

Table 1. Characteristics and treatment of 28 patients with NFPNET transformed into insulinoma, reported across 16 unique publications

Name (year)	Age (yr)	Gender	Duration between NF-PNET and insulinoma diagnoses	Therapies for NF-PNET	Therapies for metachronous insulinoma	Survival after insulinoma diagnosis
Sugiyama et al (2010)[11]	50	M	20 yr		Octreotide, surgery	—
Vashi et al (2011)[12]	43	F	1 yr 8 mo	Carboplatin, etoposide, FuDR, topotecan, TACE, sunitinib	Somatostatin, diazoxide, prednisone	Alive
Koshy et al (2013)[13]	56	F	4 yr 6 mo	Surgery	Dizoxide, TACE, octreotide, MWA	Alive
Ohn et al (2013)[8]	46	F	4 mo	Sunitinib	Steroids, TACE, streptozocin, adriamycin	—
Arslan et al (2015)[14]	62	M	2 yr	—	—	—
Fountas et al (2015)[15]	64	M	2 yr 6 mo	Everolimus, octreotide, sunitinib	Diazoxide, methylprednisone, IV glucagon infusion, streptozocin, adriamycin	Alive

Table 1. (***continued***)

Name (year)	Age (yr)	Gender	Duration between NF-PNET and insulinoma diagnoses	Therapies for NF-PNET	Therapies for metachronous insulinoma	Survival after insulinoma diagnosis
De Mestier et al (2015)[6]	-	-	3 yr 4 mo 3 yr 11 mo 18 yr 3 mo 2 yr 6 mo	—	—	—
Nahmias et al (2015)[2]	45	F	5 mo	Lanreotide, PRRT	Everolimus, streptozocin, DDP, 5-FU, PRRT	1 yr 6 mo
	63	M	4 yr	Lanreotide, PRRT	Everolimus, TACE, diazoxide, dexamethasone	—
Yoshioka et al (2015)[16]	69	F	5 yr 3 mo	Surgery	—	—
Crona et al (2016)[17]	74	M	1 yr 6 mo	Temozolomide	—	2 mo
	74	M	3 yr 11 mo	Streptozocin, 5-FU, platinum	—	6 mo
Lowette et al (2016)[18]	53	M	2 yr 5 mo	Cisplatin, etoposide, sunitinib	Everolimus, octreotide, diazoxide, FOLFOX, TACE	1 yr 5 mo
	31	F	1 yr 11 mo	Carboplatin, etoposide, doxorubicin, cyclophosphamide, cisplatin, octreotide, sunitinib, PRRT	Diazoxide, octreotide, everolimus, TACE	3 mo
	53	M	3 yr 1 mo	Octreotide, sunitinib, cisplatin, etoposide, PRRT	Diazoxide, octreotide	1 mo
	57	F	6 yr 5 mo	Surgery, everolimus	Octreotide, everolimus, diazoxide, TACE	Alive
Yu et al (2017)[19]	53	M	5 yr	Surgery, liver-directed therapies (unspecified)	Octreotide, surgery, FOLFOX	1 yr 6 mo
	39	F	6 yr	Surgery, chemotherapy (unspecified), PRRT, octreotide, everolimus, capecitabine, temozolomide, sunitinib, lanreotide	Everolimus, FOLFOX	Alive
Clover et al (2018)[4]	55	M	1 yr	Cisplatin, etoposide, lanreotide, capecitabine, temzolomide, radiation, sunitinib	TACE, everolimus, surgery, TACE, cabozantinib	1 yr
Juhlin et al (2019)[20]	51	F	2 yr	Lanreotide, streptozocin, 5-FU, pasireotide, everolimus, temozolamide	—	2 yr 5 mo
	61	M	6 yr	SSA, cisplatin, etoposide, PRRT, capecitabine, temozolomide, everolimus, TACE	PRRT, everolimus, TACE, pasireotide, diazoxide	1 yr
	65	F	5 yr	SSA, PRRT	Surgery, everolimus, TARE, octreotide, diazoxide, prednisolone	1 yr 7 mo
	68	F	5 yr	SSA	Everolimus, octreotide, prednisolone	6 mo
Keen et al (2020)[21]	59	F	14 yr	Surgery	Diazoxide, octreotide, surgery	Alive
Henker et al (2022)[22]	59	M	—	—	Diazoxide, SIRT	—

5-FU, 5-fluorouracil; DDP, cis-dichlorodiammineplatinum; F, Female; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; FuDR, floxuridine; M, male; IV, intraveous; MWA, microwave ablation; NFPNET, nonfunctioning pancreatic neuroendocrine tumor; PRRT, peptide receptor radionucleotide therapy; SIRT, selective internal radiation therapy; SSA, somatostatin analogue (unspecified); TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

arterial chemoembolization has been successfully attempted in nonsurgical candidates. Options for medical management and palliation include somatostatin analogues, steroids, and diazoxide, which inhibit insulin secretion by inducing potassium channels in pancreatic beta cells.[10] Compared with previous reports, the severity of hypoglycemia and refractory nature to medical treatment was somewhat unique in this case, likely in the setting of large tumor burden and rapid growth of the NET. At

the peak of his illness, the patient was requiring a continuous D50 infusion at 140 mL/hr with frequent meals despite steroids: carbohydrate loads unprecedented at our institution. Although medical therapies are first line in patients with high hepatic tumor burden like ours, liver-targeted interventions such as ablation, embolization, and/or surgery may ultimately be necessary to address refractory hypoglycemia through reduction in malignant insulin-producing cells.

In summary, we describe a 39-year-old man with NF-PNET and liver metastases found to have malignant insulinoma manifesting as new-onset hypoglycemia, which resolved temporarily with diazoxide and bland hepatic artery embolization. All patients with distant spread of primary PNETs who develop hypoglycemia should undergo evaluation for insulinoma. In nonsurgical cases, hypoglycemia may be medically managed with steroids, somatostatin analogues, and diazoxide, along with therapies to reduce tumor burden.

DISCLOSURES

Author contributions: R. Chatterjee conducted chart review and literature review to produce the initial manuscript draft and is the article guarantor. B. Ali and S.H. Nguyen led content design and manuscript revision. R. Chen and Y.H. Sada provided case report supervision and final revisions.

Financial disclosure: None to report.

Previous presentation: An abbreviated version of this case was presented as an e-Poster at ENDO 2022, June 11–14.

Informed consent was obtained for this case report.

Received July 31, 2022; Accepted December 9, 2022

REFERENCES

1. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: A population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121(4):589–97.
2. Nahmias A, Grozinsky-Glasberg S, Salmon A, Gross DJ. Pancreatic neuroendocrine tumors with transformation to insulinoma: An unusual presentation of a rare disease. *Endocrinol Diabetes Metab Case Rep*. 2015;2015:150032.
3. Chen SC, Dastamani A, Pintus D, et al. Diazoxide-induced pulmonary hypertension in hyperinsulinaemic hypoglycaemia: Recommendations from a multicentre study in the United Kingdom. *Clin Endocrinol (Oxf)*. 2019;91(6):770–5.
4. Clover T, Abdelkader A, Guru Murthy GS. Transformation of a non-secretory neuroendocrine tumor to insulinoma after treatment with Sunitinib: A case report and review of the literature. *J Oncol Pharm Pract*. 2019;25(6):1516–9.
5. Florio T. Adult pituitary stem cells: From pituitary plasticity to adenoma development. *Neuroendocrinology*. 2011;94(4):265–77.
6. de Mestier L, Hentic O, Cros J, et al. Metachronous hormonal syndromes in patients with pancreatic neuroendocrine tumors: A case-series study. *Ann Intern Med*. 2015;162(10):682–9.
7. Kimura H, Ohtsuka T, Fujimoto T, et al. Different hormonal expression patterns between primary pancreatic neuroendocrine tumors and metastatic sites. *Pancreas*. 2016;45(7):947–52.
8. Ohn JH, Kim YG, Lee SH, Jung HS. Transformation of nonfunctioning pancreatic neuroendocrine carcinoma cells into insulin producing cells after treatment with sunitinib. *Endocrinol Metab (Seoul)*. 2013;28(2):149–52.
9. Yu R. Malignant insulinoma is largely derived from nonfunctioning pancreatic neuroendocrine tumors: A contemporary view. *Pancreas*. 2020; 49(6):733–6.
10. Flatt PR, Shibier O, Szecowka J, Berggren PO. New perspectives on the actions of sulphonylureas and hyperglycaemic sulphonamides on the pancreatic beta-cell. *Diabete Metab*. 1994;20(2):157–62.
11. Sugiyama T, Kouyama R, Tani Y, et al. Giant malignant insulinoma which developed from a non-functioning pancreatic tumor over a long period of time. *Intern Med*. 2010;49(15):1573–9.
12. Vashi PG, Gupta D, Dahlk S. A unique case of a nonfunctional metastatic pancreatic neuroendocrine tumor transforming into an insulin-secreting tumor with an unusual clinical course. *Pancreas*. 2011;40(5):781–4.
13. Koshy AA, Gordon IO, Van Ha TG, Kaplan EL, Philipson LH. Metastatic insulinoma following resection of nonsecreting pancreatic islet cell tumor: A case report and review of the literature. *J Investig Med High Impact Case Rep*. 2013;1(1):2324709612473274.
14. Arslan MS, Ozbek M, Karakose M, et al. Transformation of nonfunctioning pancreatic tumor into malignant insulinoma after 3 years: An uncommon clinical course of insulinoma. *Arch Endocrinol Metab*. 2015;59(3):270–2.
15. Fountas A, Tigas S, Giotaki Z, Petrakis D, Pentheroudakis G, Tsatsoulis A. Severe resistant hypoglycemia in a patient with a pancreatic neuroendocrine tumor on sunitinib treatment. *Hormones (Athens)*. 2015;14(3): 438–41.
16. Yoshioka M, Shibata S, Uchinami H, et al. The transformation of a nonfunctioning islet cell tumor of the pancreas into a proinsulinoma under conditions of lung metastasis. *Intern Med*. 2015;54(7):785–90.
17. Crona J, Norlén O, Antonodimitrakis P, Welin S, Stalberg P, Eriksson B. Multiple and secondary hormone secretion in patients with metastatic pancreatic neuroendocrine tumours. *J Clin Endocrinol Metab*. 2016;101(2):445–52.
18. Lowette K, Verslype C, Van Cutsem E. Clinical characteristics and management of insulin-producing neuroendocrine carcinomas. *Acta Gastroenterol Belg*. 2016;79(2):321–7.
19. Yu R, Nissen NN, Hendifar A, et al. A clinicopathological study of malignant insulinoma in a contemporary series. *Pancreas*. 2017;46(1):48–56.
20. Juhlin CC, Skoglund S, Juntti-Berggren L, Karlberg M, Calissendorff J. Nonfunctioning neuroendocrine pancreatic tumors transforming to malignant insulinomas: Four cases and review of the literature. *Neuro Endocrinol Lett*. 2019;40(4):175–83.
21. Keen F, Iqbal F, Owen P, Christian A, Kumar N, Kalhan A. Metastatic insulinoma presenting 14 years after benign tumour resection: A rare case and management dilemma. *Endocrinol Diabetes Metab Case Rep*. 2020; 2020:20-0065.
22. Henker R, Lincke T, Hoffmeister A. Case report: Selective internal radiation therapy (SIRT) in a patient with hyperinsulinemic hypoglycemia due to a metastatic insulinoma with late onset of endocrine activity. *Z Gastroenterol*. 2022;60(9):1332–4.