

Insulinoma With Ambiguous Biochemistry, Positive ⁶⁸Ga-DOTA-Exendin-4 PET-CT, and Effective Endoscopic Ablation

Fernando Jia Jing Loo,¹  Melvin Kok Seng Lee,² Hian Liang Huang,³ Charles Kien Fong Vu,⁴ and Yin Chian Kon¹ 

¹Department of Endocrinology, Tan Tock Seng Hospital, Singapore 308433

²Department of Endocrinology, Woodlands Health Campus, Singapore 737628

³Department of Nuclear Medicine and Molecular Imaging, Singapore General Hospital, Singapore 169608

⁴Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, Singapore 308433

Correspondence: Yin Chian Kon, MBBS, Department of Endocrinology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: Winston_Kon@ttsh.com.sg.

Abstract

A 75-year-old female presented with fasting hypoglycemic episodes. A supervised fast ended at 72 hours fulfilling Whipple triad, with suppressed insulin and C-peptide levels, but discordantly suppressed serum β -hydroxybutyrate levels. After 21 months of recurring symptoms, a repeat fast ended at 48 hours with Whipple triad, suppressed serum β -hydroxybutyrate level, and borderline nonsuppressed C-peptide level, suggesting endogenous hyperinsulinism. Serum insulin levels were discordantly suppressed. Computed tomography (CT) of the abdomen demonstrated an enhancing 1.36 \times 0.93-cm nodule in the head of the pancreas. Endoscopic ultrasound (EUS)-guided fine-needle aspirate of the lesion derived cytology consistent with a neuroendocrine tumor, but fine-needle core biopsy returned normal pancreatic tissue. Because the results were equivocal, functional imaging with ⁶⁸Gallium-DOTA-exendin-4 positron emission tomography CT was performed, which confirmed the diagnosis of a single head-of-pancreas insulinoma. The patient declined surgical resection. Oral diazoxide therapy resulted in significant peripheral edema. Hence, EUS-guided radiofrequency ablation of the lesion was performed, and the patient remains symptom free 10 months postprocedure. This case illustrates that (1) exendin-4-based positron emission tomography may help one confidently diagnose and localize insulinoma when prior biochemical or endoscopic biopsy results are ambiguous; and (2) EUS-guided radiofrequency ablation is an efficacious alternative option to surgical resection in the frail, elderly patient with insulinoma.

Key Words: insulinoma, exendin-4 PET CT, endoscopic ultrasound-guided radiofrequency ablation

Introduction

Insulinomas are the most common functional pancreatic neuroendocrine tumor. Up to 95% are benign, isolated tumors curable via surgical resection [1–3]. Diagnosis requires demonstrating endogenous hyperinsulinemia coincident with fulfilling Whipple triad [1–3]. Current specific insulin assays do not crossreact with proinsulin or its degradation products, necessitating lowering of insulin cutoffs recommended by guidelines to increase the sensitivity of the prolonged fast [4, 5]. However, false negatives still exist. Virtually all benign insulinomas express a very high density of glucagon-like peptide-1 receptor (GLP-1R) [6]. Hence, GLP-1R-based positron emission tomography computed tomography (PET CT) utilizing exendin-4 that binds with high affinity and specificity to GLP-1R, can help with the diagnosis and localization of insulinoma to facilitate surgical cure [6]. As tumor enucleation and pancreaticoduodenectomy (Whipple procedure) may entail significant risk for morbidity and mortality, endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of pancreatic insulinomas is emerging as an alternative, less

invasive option to achieve tumor debulking and symptom alleviation. Our case, an elderly patient with insulinoma, illustrates these salient points.

Case Presentation

A 75-year-old Chinese female was referred as an inpatient for recurrent fasting hypoglycemic episodes. Twenty-one months ago, she had presented with giddiness, generalized weakness, and confusion after an overnight fast for her regular blood tests at the doctor's office. At that point, her capillary blood glucose measured as 2.8 mmol/L (50.4 mg/dL) (reference range, 3.9–5.5 mmol/L; 70–99 mg/dL). Her symptoms abated after a glucose-containing drink and her capillary blood glucose normalized to 5.3 mmol/L (95.4 mg/dL). Subsequently, a supervised fast performed outside of our facility was reported as negative to the patient (Table 1). HbA1c measured 4.8% (reference range, 4.5–5.6%). Serum IGF2 level was 360 ng/mL (49.6 nmol/L) (reference range, 333–957 ng/mL; 43.6–125 nmol/L) was normal. The patient continued to

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Table 1. Results of first prolonged fast performed at outside institution in February 2022

Results	Plasma BGL	Insulin ^b	C-peptide ^c	β-hydroxybutyrate
End of 72-h fast	37.8 mg/dL (2.1 mmol/L)	1.2 mU/L (8.3 pmol/L)	0.50 ng/mL (0.165 nmol/L)	18.74 mg/dL (1.8 mmol/L)
ES ^a criteria	<55 mg/dL (3.0 mmol/L)	≥3.0 μU/mL (18 pmol/L)	≥0.6 ng/mL (0.2 nmol/L)	<28.1 mg/dL (2.7 mmol/L)

Results	Plasma BGL		
Post IV 1-mg Glucagon Administration	10 minutes 39.6 mg/dL (2.2 mmol/L)	20 minutes 36.0 mg/dL (2.0 mmol/L)	30 minutes 25.2 mg/dL (1.4 mmol/L)

Abbreviations: BGL, blood glucose level; ES, Endocrine Society.

^aEndocrine Society (2009) biochemical criteria for adult endogenous hyperinsulinemic hypoglycemia. The fast concluded at 72 hours with symptomatic hypoglycemia and inappropriately suppressed serum β-hydroxybutyrate level, suggesting some insulin or insulin-like activity as the cause of hypoglycemia. However, serum insulin and C-peptide levels were appropriately suppressed. Following administration of IV glucagon 1 mg at the conclusion of the fast, the patient developed neuroglycopenic seizures. Abnormally low values are shown in bold italic font. Values in parentheses are International System of Units (SI).

^bInsulin measured via Becton Dxl 8000 platform using chemiluminescent microparticle immunoassay. Within-run imprecision coefficients of variation (CVs), using manufacturer's quality control materials, were below 3.7%, whereas the overall total imprecision CVs were less than 4.4%. Cross-reaction with intact pro-insulin was approximately 0.26% at 4000 pmol/L. Detection limit 0.03 mIU/L.

^cC-peptide measured via Abbott Architect i1000 platform using chemiluminescent microparticle immunoassay. Within-run imprecision coefficients of variation (CVs), using manufacturer's quality control materials, were below 2.4%, whereas the overall total imprecision CVs were less than 4.8%. Cross-reaction with intact pro-insulin was approximately 12.8% at 100 ng/mL. Detection limit 0.01 ng/mL.

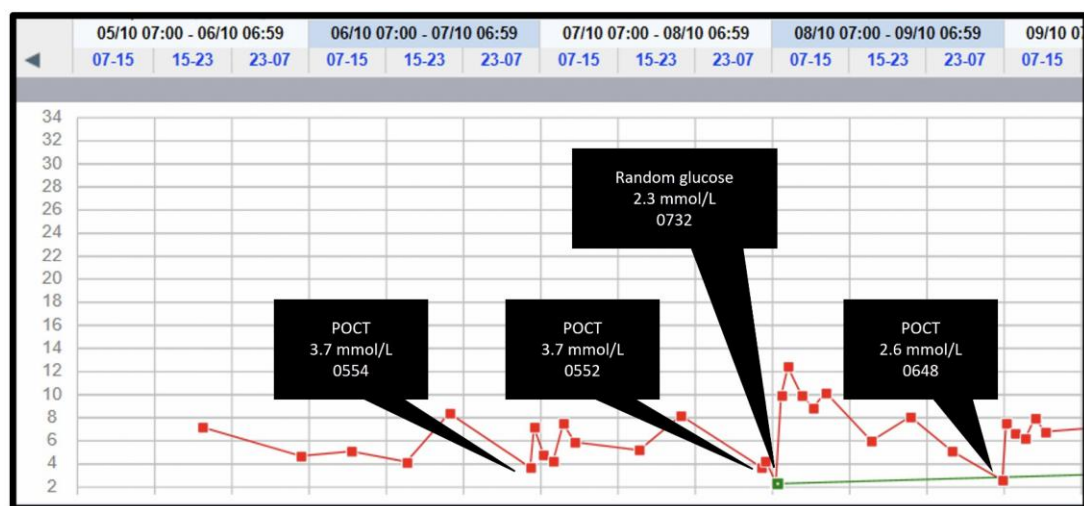


Figure 1. Inpatient capillary glucose chart demonstrating daily fasting hypoglycemia episodes. The patient was symptomatic with nonvertiginous giddiness and profound weakness during these episodes, which resolved with glucose intake.

experience the same symptoms before breakfast on a monthly basis, which would resolve with intake of food. Her last episode occurred just 1 week before the current admission. Her appetite was good and over 2 years, she had gained 9 kg in weight. She was not taking any medications. She had a Clinical Frailty Score of 5, was homebound ambulatory with a rollator frame, and used a wheelchair in the community.

Diagnostic Assessment

She weighed 61 kg, her height was 150 cm, and her body mass index was elevated at 27.1 kg/m². Physical examination was unremarkable. She had recurrent episodes of hypoglycemia both on point-of-care testing and plasma samples during her inpatient stay (Fig. 1). CT of the thorax, abdomen, and pelvis by the primary team revealed an enhancing nodular focus

measuring 1.36 cm × 0.93 cm in the head of pancreas (Fig. 2). No other focal lesion was seen. Her thyroid function, 8 AM cortisol, and renal and liver function results were all normal (Table 2). A second supervised fast at our institution terminated at 48 hours with severe weakness and inattention, hypoglycemia blood glucose level (BGL) 2.4 mmol/L (43 mg/dL), suppressed serum β-hydroxybutyrate (BOHB) levels, and borderline nonsuppressed C-peptide levels (Table 3). Serum insulin levels were again discordantly suppressed. Sulfonyleurea and insulin antibody screened as negative. Pro-insulin was not available for testing in our center. Glucagon administration was omitted because of a history of seizures at the end of her first prolonged fast.

EUS-guided biopsy of the pancreatic lesion was performed. Fine-needle aspirate cytology showed round nuclei with fine chromatin and mild nuclear anisonucleosis consistent with a

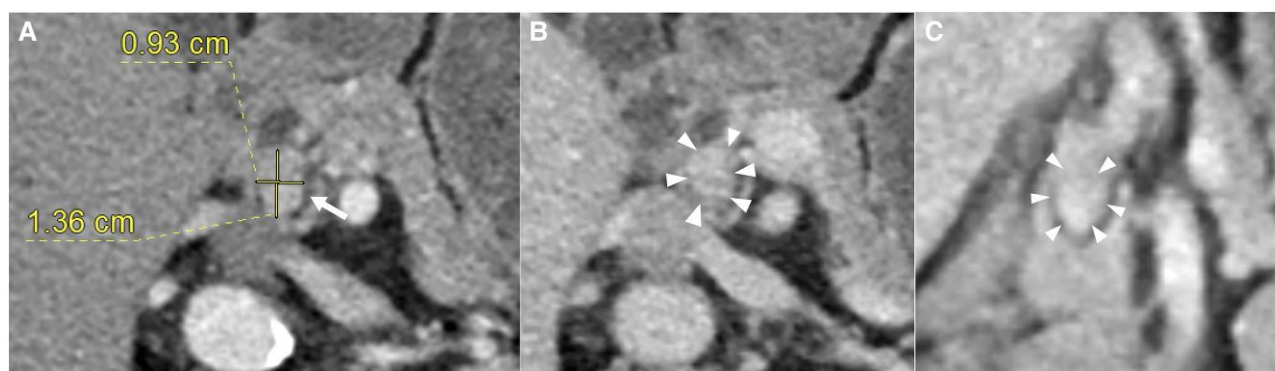


Figure 2. Computed tomography (CT) of the abdomen demonstrating a head-of-pancreas lesion. (A) Axial view, arterial phase. It appears to indent on the pancreatic duct (white arrow). (B) Axial view, venous phase (white arrowheads). (C) Coronal view, arterial phase (white arrowheads). The head of pancreas lesion shows arterial phase enhancement with venous phase washout, typical of pancreatic neuroendocrine tumor. No distal pancreatic ductal dilatation is seen.

Table 2. Results of thyroid function, 8 AM cortisol level, adjusted calcium level, and renal and liver function performed in October 2023 at our institution

Laboratory test	Free T4	TSH	8 AM cortisol	Adjusted Ca
Result	1.1 ng/dL (14 pmol/L)	2.06 mIU/L	15.8 µg/dL (438 nmol/L)	9.1 mg/dL (2.29 mmol/L)
Reference range	0.6–1.2 ng/dL (8–16 pmol/L)	0.45–4.5 mIU/L	6.7–22.6 µg/dL (185–624 nmol/L)	8.6–10.0 mg/dL (2.15–2.50 mmol/L)
Laboratory test	Creatinine ^a	Bilirubin	AST	ALT
Result	0.72 mg/dL (64 µmol/L)	0.07 mg/dL (6 µmol/L)	34 U/L	28 U/L
Reference range	0.45–0.85 mg/dL (40–75 µmol/L)	0.06–0.34 mg/dL (5–30 µmol/L)	15–40 U/L	5–40 U/L

Values in parentheses are International System of Units (SI).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, calcium; eGFR, estimated glomerular filtration rate.

^aeGFR 72 mL/min.

Table 3. Results of second prolonged fast performed in October 2023 at our institution

Results	Plasma glucose	Serum insulin ^b	C-peptide ^c	Beta-hydroxybutyrate
Start of fast	—	—	—	1.04 mg/dL (0.1 mmol/L)
End of 48-h fast	43.2 mg/dL (2.4 mmol/L)	1.8 mU/L (12.5 pmol/L)	0.72 ng/mL (0.238 nmol/L)	10.41 mg/dL (1.0 mmol/L)
ES ^a criteria	<55 mg/dL (3.0 mmol/L)	≥3.0 µU/mL (18 pmol/L)	≥0.6 ng/mL (0.2 nmol/L)	<28.1 mg/dL (2.7 mmol/L)

Abbreviation: ES, Endocrine Society.

^aEndocrine Society (2009) biochemical criteria for adult endogenous hyperinsulinemic hypoglycemia. Proinsulin was not performed. The fast terminated at 48 hours with symptomatic hypoglycemia, borderline nonsuppressed serum C-peptide level, and suppressed serum β-hydroxybutyrate level, compatible with a diagnosis of endogenous hyperinsulinism. However, serum insulin levels were discordantly suppressed. Renal function was normal. The samples were not hemolyzed, lipemic, nor icteric. Abnormally high values are shown in bold font, abnormally low values in bold italic font. Values in parenthesis are International System of Units (SI).

^bInsulin measured via Abbott Alinity i-series chemiluminescent microparticle immunoassay. Within-run imprecision coefficients of variation (CVs), using manufacturer's quality control materials, were below 1.8%, whereas the overall total imprecision CVs were less than 1.8%. Crossreaction with intact pro-insulin was approximately <0.001% at 10 000 pmol/L. Detection limit 0.4 mIU/L.

^cC-peptide measured via Abbott Alinity i-series chemiluminescent microparticle immunoassay. Within-run imprecision coefficients of variation (CVs), using manufacturer's quality control materials, were below 2.9%, whereas the overall total imprecision CVs were less than 3.3%. Cross-reaction with intact pro-insulin was approximately 12.8% at 100 ng/mL. Detection limit 0.03 ng/mL.

neuroendocrine tumor, but fine-needle core-biopsy returned normal pancreatic tissue. Despite the absence of elevated serum insulin levels and unhelpful fine-needle core-biopsy, her

characteristic history, slightly elevated C-peptide level, suppressed BOHB level, and cytology that was suggestive of neuroendocrine tumor, prompted us to evaluate further for

pancreatic insulinoma. ^{68}Ga -DOTA-exendin-4 PET CT was performed, demonstrating a single intense focal tracer uptake at the head of pancreas corresponding to the nodular

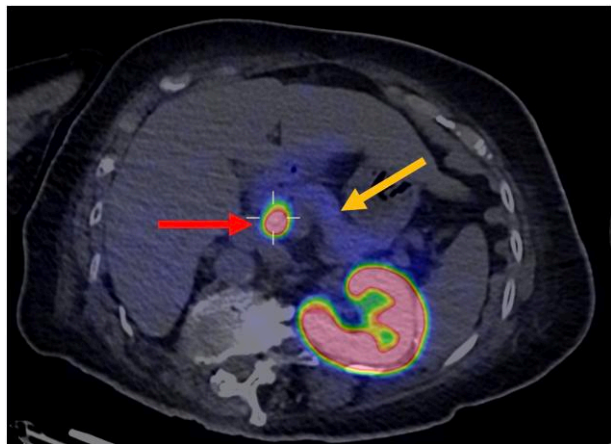


Figure 3. Positron-emission computed tomography (PET-CT) imaging was performed from the vertex of the skull to the upper thighs at 75 minutes after IV administration of 4.0 mCi ^{68}Ga -DOTA-exendin-4. Dedicated upper abdominal images were acquired at approximately 150 minutes, demonstrating presence of a tracer-avid lesion, with maximum standardized uptake value (SUVmax) 80.1 at the head of pancreas, marked with a crosshair and red arrow. The rest of the pancreas demonstrates diffuse physiological tracer uptake as marked by yellow arrow. The patient's capillary blood glucose was monitored for the duration of the process due to documented risk of hypoglycemia in patients with insulinomas receiving exendin-4. No episodes of hypoglycemia were documented.

lesion seen on initial CT scan, confirming the diagnosis of head-of-pancreas insulinoma (Fig. 3).

Treatment

The patient was advised to have small frequent meals with adequate complex carbohydrates. Oral diazoxide was initiated at 100 mg twice daily but had to be discontinued after 2 weeks because the patient developed generalized edema. In view of her age, frail status and insulinoma indenting the pancreatic duct, the patient was offered and opted for EUS-guided RFA. This was performed 2 months after the second prolonged fast, under anesthesia monitoring. As the lesion was 8 mm in width along the axis of the RFA needle entry (Fig. 4A), a shorter 5-mm active tip was chosen, to avoid ablation beyond the confines of the tumor, which may increase the risk of pancreatitis. Unlike for a malignant tumor, whereby complete tumor ablation is desired, we aimed to debulk enough to curtail the excessive endogenous insulin secretion and alleviate her symptoms of hypoglycemia. Four fanning passes were performed along the length of the tumor (Fig. 4B), with 10 to 15 watts of RFA current at 10-second intervals (Fig. 4C). Contrast enhancement with Sonovue, which was present before the RFA, showed much reduced uptake after the RFA (Fig. 4D, E).

Outcome and Follow-up

We compared her continuous glucose monitoring profile before and after EUS-RFA. Her hypoglycemia episodes had

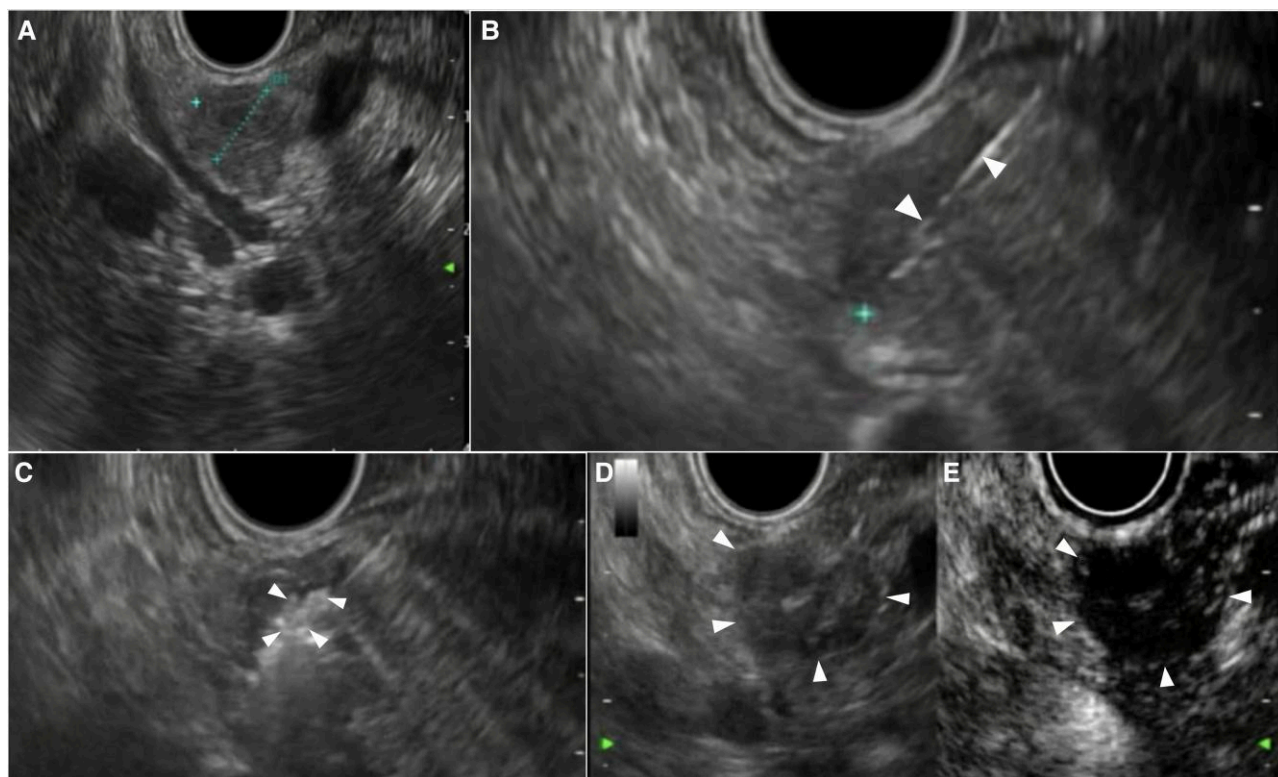


Figure 4. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) using a 19G RFA electrode (STARMed EUSRA, Taewoong Medical, Korea) with a 5-mm active tip connected to an RFA generator. (A) The hypoechoic head-of-pancreas insulinoma was measured as 8 mm in depth. (B) The hyper-echoic RFA needle (arrowheads) is passed into the center of the tumor. (C) RFA caused a microbubble appearance (arrowheads) from the boiling/thermal ablation of tissue. (D) Normal B-mode EUS showing the hypoechoic tumor (arrowheads) after RFA. (E) Sonovue (Bracco, Italy)-enhanced EUS showing no uptake in the tumor after RFA (arrowheads) whilst the surrounding normal tissue was enhanced.

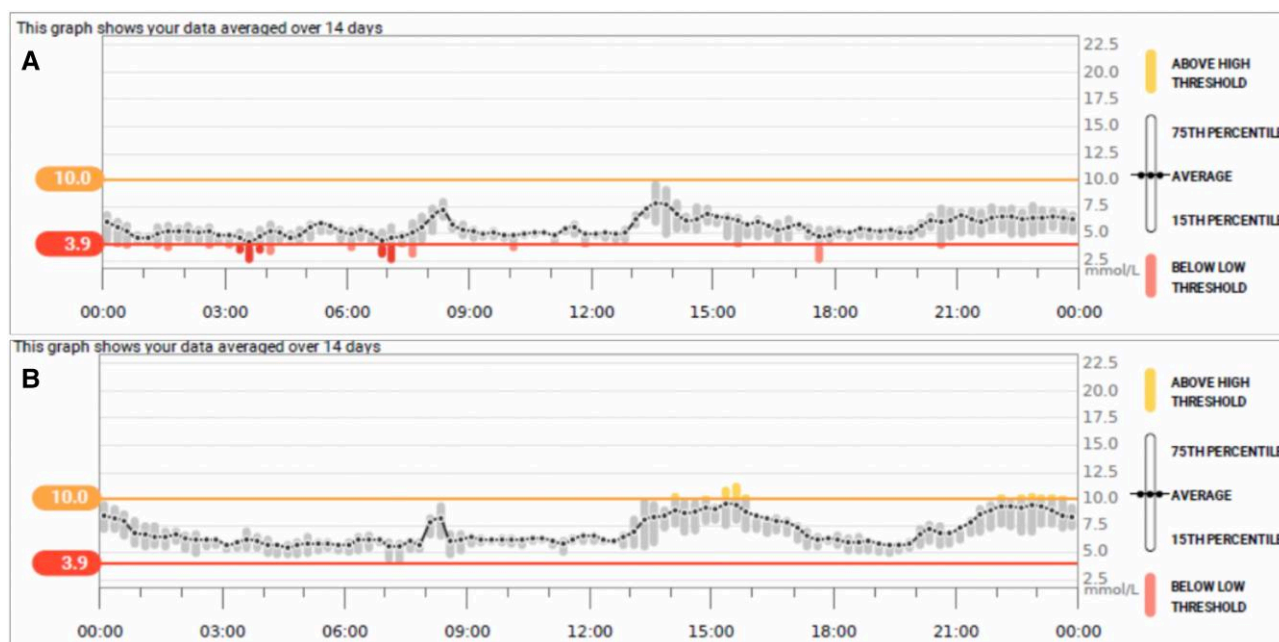


Figure 5. Continuous glucose monitoring (CGM) was done (A) 14 days pre- and (B) 14 days post endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of the head-of-pancreas insulinoma. Before EUS-RFA, CGM recorded overnight as well as premeal fasting hypoglycemic episodes. Immediately following the EUS-RFA, repeat CGM recorded no episodes of hypoglycemia.

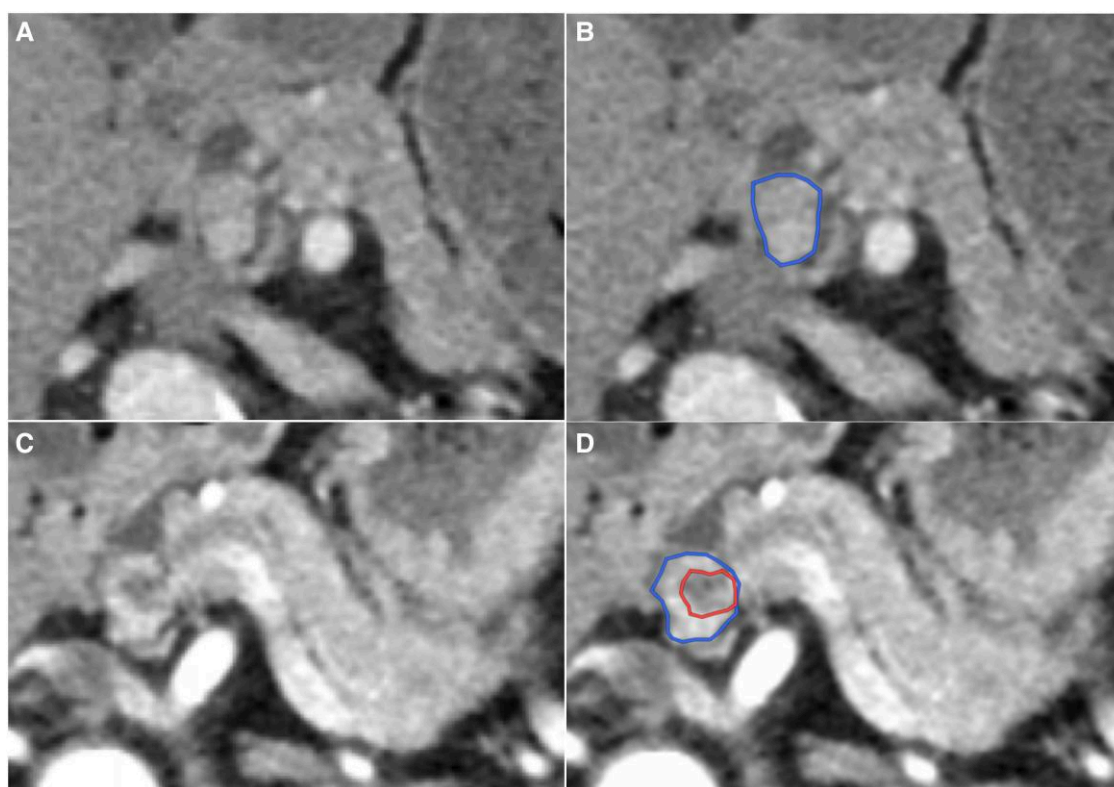


Figure 6. Computed tomography scans show (A) the tumor before radiofrequency ablation (RFA); (B) margins of the tumor in blue before RFA; (C) tumor after RFA; (D) margins of the tumor in blue and margins of the ablated zone in red after RFA.

resolved, and average interstitial glucose levels had increased (Fig. 5). CT of the pancreas 6 weeks after EUS-RFA revealed a stable pancreatic head lesion with reduced contrast enhancement in the center (Fig. 6). The patient has remained free of hypoglycemia 10 months postprocedure.

Discussion

Endogenous hyperinsulinemic hypoglycemia is diagnosed when the Whipple triad is fulfilled and concentrations of insulin, C-peptide, or proinsulin are inappropriately high for the prevailing hypoglycemia [1-3]. To avoid diagnostic

Table 4. Sensitivity and specificity of end-of-fast insulin, C-peptide, and proinsulin according to Endocrine Society criteria for endogenous hyperinsulinism, applied to different cohorts

Reference	Insulin Assay Method/% cross reaction with pro-insulin	N Insulinoma/ controls	Insulin Ss Sp	C-peptide Ss Sp	Proinsulin Ss Sp
[13] Placzkowski et al, 2009	Not specified	69/20	93% 95%	100% 60%	100% 68%
[11] Ahn et al, 2014	IRMA/0.3% 40%-1 patient	14/18	100% 72% (73-100) (46-89)	100% 83% (73-100) (58-96)	--
[9] Yu et al, 2022	ICMA/0%	144/40	100% 83%	100% 80%	97% 78%
[5] Vezzosi et al, 2003	IRMA/0%	15/-	BGL < 2.5 mmol/L 67% -	100% -	100% -
[10] Vezzosi et al, 2007	IRMA and ICMA/ 0% for both assay methods	31/47	BGL 2.5-3.3 mmol/L IRMA 56% 50% ICMA 81% 45%	90% 55%	97% 42%
		33/4	BGL < 2.5 mmol/L IRMA 65% - ICMA 89% -	97% 100%	100% 100%

Abbreviations: (), 95% confidence interval; ICMA, automated immunochemiluminometric assay; IRMA, immunoradiometric assay; Sp, specificity; Ss, sensitivity.

misclassification, neuroglycopenic symptoms or signs must be present to end the fast, together with a low BGL [7]. For instance, in normal women, plasma glucose value may fall below 40 mg/dL (2.2 mmol/L) during a prolonged fast, but this is associated with low or undetectable insulin concentrations and no neuroglycopenic symptoms [8]. From case-control studies, noninsulinoma patients do not reach BGL < 2 mmol/L (36 mg/dL) during a prolonged 72-hour fast; such an occurrence should raise our suspicion of insulinoma [9-12].

At the end of the prolonged fast, patients with insulinoma demonstrate significantly lower mean plasma glucose level and significantly higher mean insulin and C-peptide levels than controls [7, 9-12]. Serum insulin level is positively correlated with end-of-fast (EOF) BGL in normal controls and negatively correlated in patients with insulinoma. Hence, the separation in insulin level between the 2 groups is clearer when EOF-BGL are lower—for example below 2.5 mmol/L (45 mg/dL) [9-13]. However, even when EOF-BGL are below 2.5 mmol/L (45 mg/dL), a minority of patients with insulinoma demonstrate low insulin levels that overlap with controls, potentially leading to false-negative diagnosis [5,10, Table 4].

In their cohort of 18 patients with insulinoma and 46 controls, Dauben et al compared diagnostic performance by Endocrine Society (ES) criteria (BGL < 55 mg/dL [3.1 mM], insulin \geq 3 mIU/L, C-peptide \geq 0.6 ng/mL [200 pmol/L], and proinsulin \geq 5 pmol/L) with European/North American Neuroendocrine Tumor Society criteria (BGL \leq 40 mg/dL [2.2 mM], insulin \geq 6 mIU/L, the rest identical) [14]. Diagnostic sensitivity was higher by ES criteria (94% vs 78%) but specificity was lower (89% vs 100%). Thus, one might expect to improve specificity but reduce sensitivity when a lower BGL cutoff and higher insulin cutoff are used [13, 14].

Insulinomas produce proinsulin that were detected in the older polyclonal antibody insulin assays that had as much as 40% to 80% crossreactivity with proinsulin. Current monoclonal antibody insulin assays do not detect proinsulin or its metabolites [15]; thus, reducing the cutoff from 6 mIU/L to

3 mIU/L has been necessary to maintain diagnostic sensitivity nearer 100%. When ES criteria utilizing specific insulin assays are applied to various cohorts, generally all 3 β -cell peptides (insulin, C-peptide, proinsulin) individually demonstrate good sensitivity (Table 4), but specificity is improved when more peptide threshold criteria are met [9-11]. By ES criteria, EOF insulin levels by specific assays may be falsely low in 10% to 20% of patients (Table 4), but a concomitantly high C-peptide, high proinsulin, or low BOHB level will indicate correctly the presence of insulinoma [10, 13, 16, 17].

For both fasts, our patient showed anomalously low EOF insulin levels (Tables 1 and 3). This may be due to delayed collection of samples (pulsatile secretion by tumor, first-pass hepatic clearance with very short circulating half-life of insulin (4-6 minutes) [18, 19], sample hemolysis (not in this case) [5], lower insulin secretion from insulinomas smaller than 1.4 cm (as in this case) [5], and predominantly proinsulin-secreting insulinomas [5, 10, 20-23]. Proinsulin itself may decrease hepatic gluconeogenesis [24]. Proinsulinoma should be suspected when low insulin levels measured by a highly specific insulin assay coexist with hypoglycemia. Then, inappropriate high-normal C-peptide level (Table 3), with its longer circulating half-life (30-40 minutes), and low EOF BOHB level may provide corroborating evidence of endogenous hyperinsulinism (Tables 1 and 3). To avoid a false-negative diagnosis when using specific insulin assays, it is prudent to measure both C-peptide and proinsulin concomitantly [5, 10, 20-22].

Rarely, both EOF insulin and C-peptide levels measure below ES threshold criteria for endogenous hyperinsulinism (Table 1), potentially leading to a false-negative diagnosis [19]. In such cases, where proinsulin levels are not available, low EOF BOHB level reflects ongoing insulin or insulin-like mediated antilipolytic activity and should not be overlooked (Tables 1,3), but rather prompt further investigation once fasting noncompliance has been excluded [13, 16, 17]. At the end of the first prolonged fast, our patient's BGL did not increase by 1.4 mmol/L or more after IV glucagon 1 mg,

which would reflect glycogenic and antiglycogenolytic effect of insulin [16]. We speculate that her EOF seizure may have led to immediate glycogen depletion that resulted in a discordantly negative IV glucagon test.

Because of overexpression of GLP1R by insulinomas, GLP1R-based imaging has been developed utilizing exendin-4 as the glucagon-like peptide analogue. Exendin-4 has a sensitivity of 68.8% to 95% to detect insulinomas, depending on the radionuclide paired to it. In particular, ^{68}Ga exendin-4 PET CT has demonstrated a sensitivity of 96.9% and specificity of 100% in detecting benign insulinomas [6, 25]. Our case demonstrated clear isotope uptake that corresponded to the head-of-pancreas nodule on anatomic CT imaging.

Head-of-pancreas insulinomas may be surgically removed by enucleation or require Whipple resection. As her insulinoma was indenting the pancreatic duct, even enucleation entailed significant risk of pancreatic fistula and abdominal abscess formation [26]. Because of our patient's advanced age and frailty, and because most insulinomas are benign, we considered debulking by EUS-guided RFA to achieve remission of hypoglycemia to be a safer option [27]. Systematic reviews report good biochemical response with an increase in average monitored glucose levels and reduction in episodes of hypoglycemia reported by patients [28].

In a large retrospective study, Crino et al compared the outcome of 89 patients with pancreatic insulinoma treated with EUS-RFA against 89 patients who underwent surgical resection, matched by propensity scoring for age, lesion size, site, grade, and distance to main pancreatic duct [27]. Fifteen of 89 patients (16.9%) treated with EUS-RFA experienced symptom relapse, 12 within 1 year. Four of these patients underwent uneventful patient-preferred surgical resection, whereas 11 were successfully retreated with a repeat EUS-RFA session with complete symptom resolution lasting for an additional mean follow-up period of 23 months. Evidence of residual vascularized tissue was more frequent in patients with symptom recurrence than in patients without (8/15; 53.3% vs 5/74; 6.8%, $P < .0001$). Our patient was informed of her subtotal ablation and was receptive to a repeat EUS-RFA should her symptoms recur.

Learning Points

- When insulinoma is highly suspected and insulin levels are anomalously low, one should consider corroborative data such as neuroglycopenic symptoms, concomitantly elevated C-peptide, elevated pro-insulin, and low BOHB levels to assess the overall likelihood of insulinoma.
- In equivocal cases, GLP-1R-based imaging, such as with ^{68}Ga -DOTA-exendin-4 PET CT, may help to diagnose and localize insulinomas.
- Endoscopic ablation may be a suitable alternative treatment modality for the frail, elderly patient with insulinoma.

Contributors

All authors made individual contributions to authorship. F.J.J.L., M.K.S.L., and Y.C.K. were involved in the diagnosis and management of the case. F.J.J.L., C.K.F.V., H.L.H., and Y.C.K. participated in the preparation of parts of manuscript. H.L.H. oversaw and reported on the ^{68}Ga -DOTA-Exendin-4 PET-CT scan. C.K.F.V. performed the endoscopic radiofrequency ablation. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent has been obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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):709-728.
2. Vinik AI, Woltering EA, Warner RR, *et al.* NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas.* 2010;39(6):713-734.
3. Jensen RT, Cadiot G, Brandi ML, *et al.* ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology.* 2012;95(2):98-119.
4. Wiesli P, Brändle M, Zapf J, *et al.* Assessment of hyperinsulinaemia at the termination of the prolonged fast. *Clinica Chimica Acta.* 2004;342(1-2):227-231.
5. Vezzosi D, Bennet A, Fauvel J, *et al.* Insulin levels measured with an insulin-specific assay in patients with fasting hypoglycaemia related to endogenous hyperinsulinism. *Eur J Endocrinol.* 2003;149(5):413-419.
6. Shah R, Garg R, Majmundar M, *et al.* Exendin-4-based imaging in insulinoma localization: systematic review and meta-analysis. *Clin Endocrinol.* 2021;95(2):354-364.
7. Wiesli P, Brändle M, Schwegler B, Lehmann R, Spinass GA, Schmid C. A plasma glucose concentration below 2.5 mmol L⁻¹ is not an appropriate criterion to end the 72-h fast. *J Intern Med.* 2002;252(6):504-509.
8. Merimee TJ, Fineberg SE. Homeostasis during fasting. Hormone substrate differences between men and women. *J Clin Endocrinol Metab.* 1973;37(5):698-702.
9. Yu J, Liu Y, Lyu L, *et al.* The optimal diagnostic criteria of endogenous hyperinsulinemic hypoglycemia based on a large cohort of Chinese patients. *Front Endocrinol.* 2022;13:994707.
10. Vezzosi D, Bennet A, Fauvel J, Caron P. Insulin, C-peptide and pro-insulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. *Eur J Endocrinol.* 2007;157(1):75-83.
11. Ahn CH, Kim LK, Lee JE, *et al.* Clinical implications of various criteria for the biochemical diagnosis of insulinoma. *Endocrinol Metab.* 2014;29(4):498-504. Erratum in: *Endocrinol Metab.* 2017;32(2):306.
12. Nauck MA, Meier JJ. Diagnostic accuracy of an "amended" insulin-glucose ratio for the biochemical diagnosis of insulinomas. *Ann Intern Med.* 2012;157(11):767-775.
13. 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):1069-1073.

14. Dauben L, Simon MC, Strassburger K, *et al.* Comparison of the diagnostic accuracy of the current guidelines for detecting insulinoma. *Eur J Endocrinol.* 2019;180(6):381-386.
15. Shimizu T, Sasakuma F, Ishikawa O, Matsumiya K, Hasegawa K, Sasaki A. Assessment of immunoassays for insulin in diagnostic tests for insulinoma. *Diabetes Res Clin Pract.* 1994;26(2):149-154.
16. O'Brien T, O'Brien PC, Service FJ. Insulin surrogates in insulinoma. *J Clin Endocrinol Metab.* 1993;77(2):448-451.
17. Service FJ, O'Brien PC. Increasing serum betahydroxybutyrate concentrations during the 72-hour fast: evidence against hyperinsulinemic hypoglycemia. *J Clin Endocrinol Metab.* 2005;90(8):4555-4558.
18. Coelho C, Druce MR, Grossman AB. Diagnosis of insulinoma in a patient with hypoglycemia without obvious hyperinsulinemia. *Nat Rev Endocrinol.* 2009;5(11):628-631.
19. Chammas NK, Teale JD, Quin JD. Insulinoma: how reliable is the biochemical evidence? *Ann Clin Biochem.* 2003;40(6):689-693.
20. Chia CW, Saudek CD. The diagnosis of fasting hypoglycemia due to an islet-cell tumour obscured by a highly specific insulin assay. *J Clin Endocrinol Metab.* 2003;88(4):1464-1467.
21. Gómez-Pérez FJ, Cuevas-Ramos D, Valdés PA, Aguilar-Salinas CA, Mehta R, Rull JA. Beta-cell adenomas without hyperinsulinemia with use of highly specific insulin radioimmunoassays: case report and review of literature. *Endocr Pract.* 2010;16(4):660-663.
22. Guettier JM, Lungu A, Goodling A, Cochran C, Gorden P. The role of proinsulin and insulin in the diagnosis of insulinoma: a critical evaluation of the Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2013;98(12):4752-4758.
23. Dons RF, Hodge J, Ginsberg BH, *et al.* Anomalous glucose and insulin responses in patients with insulinoma: caveats for diagnosis. *Arch Intern Med.* 1985;145(10):1861-1863.
24. Glauber HS, Henry RR, Wallace P, *et al.* The effects of biosynthetic human proinsulin on carbohydrate metabolism in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1987;316(8):443-449.
25. Jansen TJP, van Lith SAM, Boss M, *et al.* Exendin-4 analogs in insulinoma theranostics. *J Labelled Comp Radiopharm.* 2019;62(10):656-672.
26. Kimura W, Tezuka K, Hirai I. Surgical management of pancreatic neuroendocrine tumors. *Surg Today.* 2011;41(10):1332-1343.
27. Crinò SF, Napoleon B, Facciorusso A, *et al.* Endoscopic ultrasound-guided radiofrequency ablation versus surgical resection for treatment of pancreatic insulinoma. *Clin Gastroenterol Hepatol.* 2023;21(11):2834-2843.
28. El Sayed G, Frim L, Franklin J, *et al.* Endoscopic ultrasound-guided ethanol and radiofrequency ablation of pancreatic insulinomas: a systematic literature review. *Ther Adv Gastroenterol.* 2021;14:17562848211042171.