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Case Report

A Long Way to Find a Small Tumor: The Hunt for an Insulinoma

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Abstract

We report a case of a 35–year-old woman with recurrent episodes of hypoglycemia. Biochemical investigation was suggestive of hyperinsulinemic hypoglycemia, and hence a provisional diagnosis of insulinoma was made. Despite extensive investigation using magnetic resonance imaging, endoscopic ultrasound, and ^{68}Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) scanning, the tumor could not be localized. Long-distance travel allowed her to undergo a ^{68}Ga-Exendin-4 PET/CT scan that identified a lesion in the uncinate process of the pancreas, subsequently confirmed by intraoperative ultrasound. Enucleation of the 1.5-cm lesion was performed, and histopathology confirmed a well-differentiated pancreatic neuroendocrine tumor. Postoperatively, the patient has remained free of hypoglycemic episodes and has shown normalization of glucose levels. This case underscores the efficacy of ^{68}Ga-Exendin-4 PET/CT in the localization of an occult insulinoma, facilitating timely and curative surgical intervention, and the importance of patients having access to such a facility when not locally available.

Key Words: insulinoma, ^{68}Ga-Exendin-4 PET/CT, ^{68}Ga-DOTATATE PET/CT, occult insulinoma, pNET, hypoglycemia, hyperinsulinemic hypoglycemia

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasonography; GLP-1, glucagon-like peptide 1; MEN-1, multiple endocrine neoplasia; MRI, magnetic resonance imaging; PET, positron emission tomography; pNET, pancreatic neuroendocrine tumor; SACST, selective arterial calcium stimulation testing; SSTR, somatostatin receptor.

Introduction

Insulinomas are the most common functioning pancreatic neuroendocrine tumor (pNET) [1, 2] and are a frequent cause of hyperinsulinemic hypoglycemia in adults without diabetes [3]. Insulinomas comprise approximately 1% to 2% of all pancreatic tumors [4]. These tumors are predominantly benign, solitary, and usually small (<2 cm) [5-8]. Because of their smaller size, localization may be exceptionally difficult. Various modalities have been used to localize the tumor including computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). Where there is uncertainty, selective arterial calcium stimulation testing (SACST) can be used, but this regionalizes rather than localizes, is a complex procedure, and is only available in major centers [9, 10]. The sensitivity of ^{68}Ga-DOTATATE positron emission tomography (PET)/CT to identify insulinoma is only approximately 50%, although it tends to be more often positive in the presence of a metastatic tumor.

More recently, ^{68}Ga-Exendin-4 PET/CT is a recent addition to localization modalities because the majority of such tumors will express the glucagon-like peptide 1 (GLP-1) receptor on their cell surface [11-13], although it is not widely available. Here, we describe a case of an occult insulinoma that could not be localized by EUS, CT, MRI, or ^{68}Ga- DOTATATE PET/CT, which was ultimately identified by ^{68}Ga-Exendin-4 PET/CT following a transnational referral, allowing for successful curative surgery.

Case Presentation

A 35-year-old woman from the United Kingdom, who was working as a chemistry teacher in Dubai, sought consultation in London in early 2024 in the light of recurrent episodes of hypoglycemia. Two years previously, she had experienced an episode of what was considered "acute labyrinthitis," at which time when she was first noted to have low plasma glucose levels (28 mg/dL; 1.5 mmol/L). She recalled that for the past 2 years she had often developed tremors before lunch, which improved with sugar intake, and she developed sweating, palpitations, and confusion if she missed meals. She

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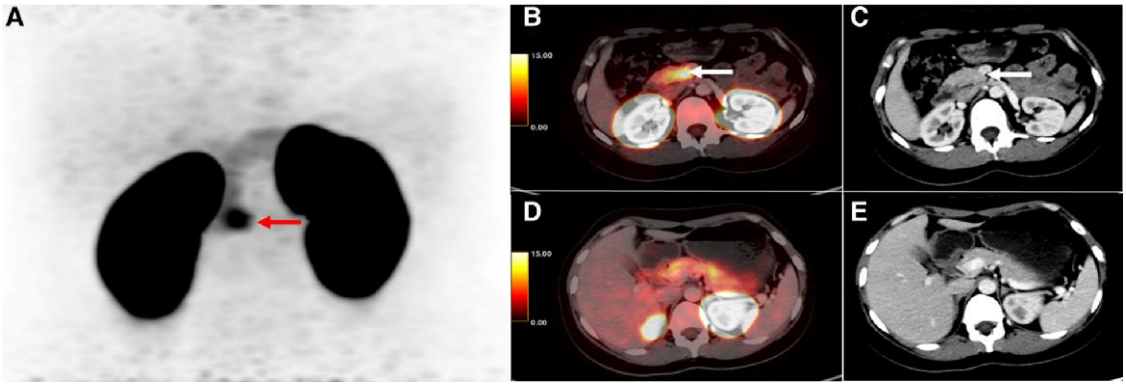

Figure 1. Maximum intensity projection (MIP) image of regional ^{68}Ga-exendin PET (A) showing focal tracer uptake in the region of the uncinate process of pancreas with mild diffuse uptake in the rest of the pancreas. Axial fused PET/CT image (B) showing focal tracer uptake (SUVmax 21.8) in the uncinate process of the pancreas with an inapparent lesion on corresponding CT image (C). Mild diffuse uptake was seen in the rest of the pancreas (D and E).

therefore had started taking frequent meals to avoid such episodes, and also reported 10-kg weight gain over the previous 18 months. She is a nonsmoker and does not drink alcohol. Her family history includes type 2 diabetes in her father (who had died 2 years previously), and rheumatic heart disease in her mother. Her body mass index was 23.

Diagnostic Assessment

She initially consulted an endocrinologist in Dubai in June 2023, where a fasting glucose was 2.2 mmol/L (40 mg/dL). A 72-hour fasting test revealed hypoglycemia within 2 to 3 hours, with inappropriately high insulin, pro-insulin, and C-peptide levels, and suppressed β-hydroxybutyrate, indicating hyperinsulinemic hypoglycemia. Her serum cortisol was 276 nmol/L (10 μg/dL). She then sought consultation with a physician in London: her fasting blood glucose was 2.1 mmol/L (38 mg/dL): an abdominal ultrasound was normal, whereas magnetic resonance cholangiopancreatography also failed to reveal any pancreatic lesion.

On returning to Dubai in November 2023, she underwent another prolonged fast test with similar results, becoming hypoglycemic at 4 hours with elevated insulin and C-peptide levels. A contrast-enhanced 3T-MRI of the abdomen also failed to detect any pancreatic abnormality. A screen for sulfonylureas was negative. She proceeded to a ^{68}Ga-DOTATATE PET/CT and EUS, neither of which identified any pancreatic lesion. She therefore continued taking frequent small meals and used a Freestyle Libre-2 sensor patch to alert her to imminent hypoglycemia, when she would take an additional high-carbohydrate snack.

In January 2024, she consulted through a video conference at London, where a new EUS was arranged, and carried out in February 2024: a possible 4-mm lesion was identified in the uncinate process of the pancreas, but cytology of the lesion simply revealed normal pancreatic tissue. She was started on diazoxide therapy, 50 mg thrice a day, but found this difficult to tolerate.

It was therefore decided to see whether a ^{68}Ga-Exendin-4 PET scan could be organized. This is not available in the United Kingdom, and although this has been available on occasion in the Netherlands, for organizational reasons this would not be possible for some months. However, this was currently operationally available in Chandigarh, India. She therefore travelled from Dubai to India: in May 2024, the ^{68}Ga-Exendin-4 PET/CT scan identified a single focal tracer-avid lesion, which on CT co-registration was localized to the uncinate process of the pancreas (Fig. 1).

Treatment

In the light of the positive scan, the patient returned to Dubai and consulted a specialist, hepatobiliary pancreatic surgeon. She underwent laparotomy with intraoperative ultrasound, which confirmed a 1.5-cm lesion in the corresponding area in the uncinate process. Enucleation of the lesion was performed. A portal venous blood sample was measured for insulin levels during surgery. Before the excision of the tumour, the portal venous insulin level was 142.8 μU/mL (normal range, 2.6-24.9 μU/mL). Following the excision of the tumor, her portal venous blood was measured after 30 minutes when the insulin level had fallen to 14.36 μU/mL. The frozen section also confirmed the complete removal of the tumor.

Outcome and Follow-up

Final histopathology of the excised lesion demonstrated a well-differentiated grade 1 pNET, with immunohistochemistry studies showing cytoplasmic positivity by tumor cells for synaptophysin and insulin, with a Ki-67 proliferation index of 1%. Immunohistochemistry for somatostatin receptor subtype 2 showed 2+ intensity cytoplasmic positivity in 60% tumor cells, whereas it was negative for the subtype 5 receptor (Fig. 2A-F). Postoperatively, she has experienced no further hypoglycemic episodes, with a weight loss of 4.5 kg in 1 month. Follow-up continuous glucose monitoring showed a mean blood glucose level of 7 mmol/L (126 mg/dL). Currently, after 6 months of follow-up, she has shown no further episodes of hypoglycemia, either clinically or biochemically.

Discussion

We report a case of an occult insulinoma that required multiple imaging modalities and consultations for localization, yet conventional imaging failed to identify the lesion. Localizing a biochemically confirmed insulinoma is crucial because surgical excision can cure the condition [1, 2]. However, localization is particularly challenging when the tumor is smaller than 2 cm, as seen in the index case [13].

Our patient exhibited symptoms of hypoglycemia that were confirmed with low plasma glucose levels and resolved with

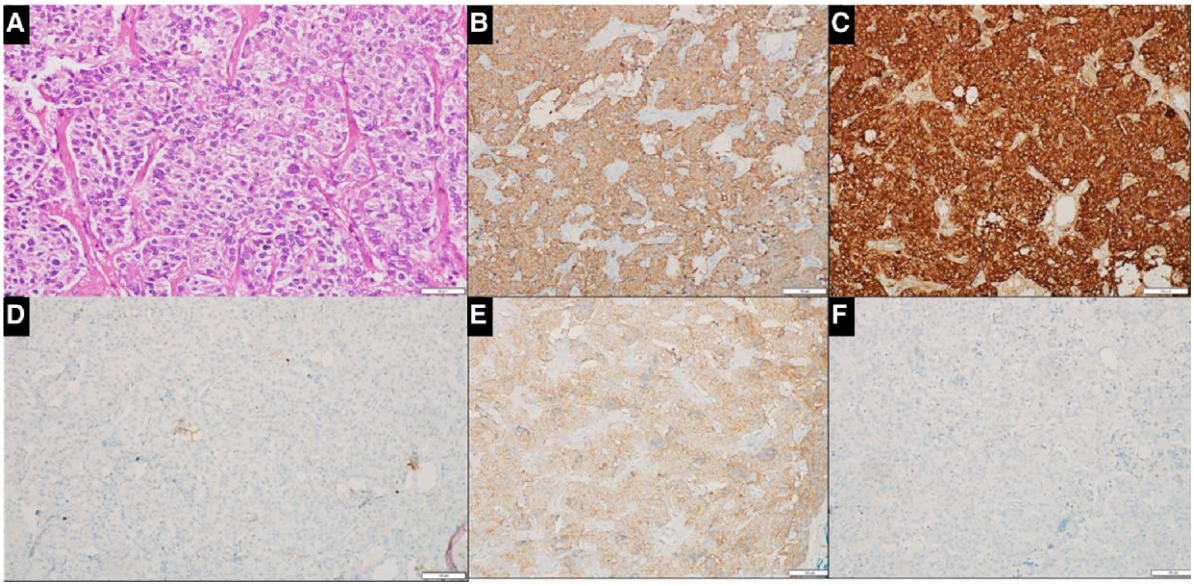

Figure 2. Hematoxylin and eosin (H&E)-stained sections (magnification: 40×) showing circumscribed tumors arranged in nests and trabeculae, with individual tumor cells are monomorphic with round nuclei, stippled chromatin, inconspicuous nucleoli, and moderate granular eosinophilic cytoplasm. Neuroendocrine tumor grade I. Immunohistochemistry (IHC) studies show cytoplasmic positivity by tumor cells for synaptophysin (B) and insulin (C) with Ki67 proliferation index of 1% (D). IHC for SSTR2 (E) shows 2+ intensity cytoplasmic positivity in 60% tumor cells, whereas it is negative for SSTR5 (F).

treatment, satisfying the Whipple triad [14]. The majority of patients with insulinoma (73%-80%) typically exhibit fasting hypoglycemia, as seen in the index case; however, 6% of patients present only with postprandial hypoglycemia, whereas 21% may experience both [15, 16]. These patients often eat frequent meals to avoid symptomatic hypoglycemia, which can lead to weight gain, which may also relate to the hyperinsulinemia [17]. In our case, the patient experienced a 10-kg increase in weight over the past 1.5 years. Elevated insulin and C-peptide levels during hypoglycemia indicate endogenous hyperinsulinemic hypoglycemia, as observed in the index case, although it is interesting that the elevation in C-peptide and pro-insulin levels were more prominent than insulin, showing that these measurements may be more diagnostic then simply insulin [18]. It is important to screen for sulfonylurea during episodes of hypoglycemia, as we did with our patients, because sulfonylurea use can also result in elevated insulin and C-peptide levels. Blood ketone levels are suppressed in patients with hyperinsulinemic hypoglycemia, serving as a surrogate marker for hyperinsulinemia. The causes of endogenous hyperinsulinemic hypoglycemia include insulinoma, noninsulinoma pancreatogenous hypoglycemia syndrome, postbariatric surgery, and autoimmune hypoglycemia [2].

After documenting endogenous hyperinsulinemic hypoglycemia, the next step is to localize the tumor using various noninvasive and invasive modalities. Cross-sectional imaging is often useful, with contrast-enhanced CT offering a sensitivity of 63% to 94% [10]; contrast-enhanced MRI has a sensitivity of 60% to 90% for localizing the tumor and involves no radiation exposure, unlike contrast-enhanced CT [19]; abdominal ultrasound is not very sensitive, with a published sensitivity ranging from 9% to 63% [10] (Table 1). Nevertheless, in 25% to 35% of cases, such conventional imaging modalities such EUS, CT, and MRI fail to localize the lesion [21]. For patients in whom such conventional imaging fails to localize the lesion, options for localization include EUS, functional imaging such as ^{68}Ga-DOTATATE PET/CT, or SACST. As a last resort, the surgeon can go in "blind" and possibly perform intraoperative ultrasound. EUS has a sensitivity ranging from 40% to 93% with an excellent visualization of the head of the pancreas, although visualization of the tail of the pancreas can be challenging. It can help in obtaining a concurrent guided biopsy from the tumor [10]. This can be especially helpful in patients with multiple endocrine neoplasia (MEN-1), in which multiple, smaller NETs of the pancreas are likely to occur. SACST has a sensitivity of 67% to 100%, but is invasive, technically challenging, and only localizes the arterial territory from which insulin is secreted ("regionalization"), without providing the exact anatomical localization of the tumor [10, 22]. In our case, modalities such as ultrasound, CT, MRI, and EUS all failed to localize the lesion. The suspicious

Table 1. Sensitivity and specificity of various modalities used for the diagnosis of insulinoma [10, 20]

Modality	Sensitivity	Specificity
Transabdominal USG	9%-63%	—
Computed tomography	63%-94%	75%
MRI	60%-90%	65%
Endoscopic USG	40%-93%	90%
SACST	63%-100%	86%
^{68}Ga-DOTATATE PET/CT	32%-90%	14%
^{68}Ga-Exendin-4 PET/CT	84.6%	100%
Intraoperative inspection and palpation by surgeon	77%-91%	—
Intraoperative USG	91%-93%	—

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SACST, selective arterial calcium stimulation testing; USG, ultrasonography.

lesion in the pancreas detected during EUS in our patient was unlikely to have been the cause, as the lesion was only 4 mm and the fine needle aspiration cytology results indicated normal pancreatic tissue.

Insulinomas express both somatostatin receptors (SSTR), especially SSTR-2, and also GLP-1 receptors. Hence, functional imaging targeting these receptors can be used to localize occult insulinomas. In contrast to other pNETs, insulinomas generally express less SSTRs, resulting in false-negative ^{68}Ga- DOTATATE PET/CT scans, as seen in the negative scan in our case [23, 24]. The sensitivity of ^{68}Ga-DOTATATE PET/CT to detect insulinoma ranges from 32% to 90% [23], approximately 40% according to 1 metanalysis [25], although 2 advantage of ^{68}Ga- DOTATATE PET/CT is that this scan can be used to pick up other tumors such as parathyroid adenomas, pituitary tumors, or pNETs associated with MEN-1.

Exendin-4 is a GLP-1 analogue that was introduced for the treatment of diabetes mellitus. The GLP-1 receptor is highly expressed on insulinomas and hence ^{68}Ga-Exendin-4 PET/CT has been investigated to localize insulinomas, as 98% of benign insulinomas express GLP-1R, with tumor cells expressing the receptor at a density 5 times higher than that of normal β cells [23, 26]. Malignant insulinomas predominantly overexpress somatostatin type 2 receptors and have a lower expression of GLP-1 receptors compared to benign tumors [27]. Therefore, for patients with malignant insulinomas, ^{68}Ga- DOTATATE PET/CT is more sensitive than ^{68}Ga-Exendin-4 PET/CT [27]. Because of SSTR overexpression in these tumors, peptide receptor radionuclide therapy can be considered as a treatment option in inoperable cases, although peptide receptor radionuclide therapy using exendin-4 as the labelled treatment ligand is not used for tumors expressing GLP-1R because of its high renal uptake and associated side effects [27]. The other advantage of this imaging is that it can provide an assessment of the whole body, which can help localize metastatic lesions, multiple pancreatic lesions, or lesions in extrapancreatic locations [20].

Previously published literature on patients with MEN-1 and insulinomas showed that ^{68}Ga-Exendin-4 PET/CT had a sensitivity of 84.6%, a specificity of 100%, and an overall accuracy of 94.6%, whereas MRI had a sensitivity of 38.5%, specificity of 100%, and accuracy of 78.4% [28, 29]. Combining MRI with ^{68}Ga-Exendin-4 PET/CT increased the sensitivity to 92.3% compared to ^{68}Ga-Exendin-4 PET/CT (84.6%) [28]. However, some nonfunctional pNETs can also express GLP-1 receptors [23], and studies have reported tracer uptake with ^{68}Ga-Exendin-4 PET/CT in patients with nonfunctional pNETs [28]. Conversely, other functioning tumors, such as gastrinomas and pancreatic polypeptide-producing tumors are less likely to express GLP-1R and do not show tracer avidity in ^{68}Ga-Exendin-4 PET/CT [23, 28].

The availability of ^{68}Ga-Exendin-4 PET/CT is currently limited, but its availability in certain countries and centers means that there is still an opportunity for patients to access this modality in some circumstances. Although the term "medical tourism" has been used in a negative sense, where there is very limited availability of a well-substantiated diagnostic or therapeutic maneuver, such travel beyond state or national boundaries can have positive benefits and provide opportunities for more accessible and affordable tumor localization for patients facing these limitations. In this case, the patient traveled a considerable distance to undergo a ^{68}Ga-Exendin-4 PET/CT, resulting in faster tumor localization and surgical excision, and a positive boost to her quality of life following surgical removal. Utilization of such Centers of Excellence may improve tumor localization in a cost-effective way.

Learning Points

- Insulinomas are rare but need to be suspected when confirmed hypoglycemia is associated with inappropriate insulin and C-peptide levels, and no other drug-related cause.
- These tumors can be extremely small and not easily imaged even on state-of-the-art CT, MRI, and EUS. Radionuclide scanning with ^{68}Ga-exendin-4 PET/CT can locate such tumors when all other modalities have failed.
- Where such imaging is not locally available, there may be other national or transnational centers that have the relevant facility, and international travel may aid in the identification of appropriate imaging availability.

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Contributors

All authors made individual contributions to authorship. D.A., A.G., P.D., and H.S. were involved in the diagnosis and management of the patient and manuscript submission. A.B. was involved in histopathology sectioning and preparation of histology images. R.R. was responsible for the patient's surgeries. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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