The occult insulinoma was localized using endoscopic ultrasound guidance:A case report

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The occult insulinoma was localized using endoscopic ultrasound guidance:A case report

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Key Clnical Message

The case report aim to deepen primary care clinicians' understanding of insulinoma. We advocate for invasive EUS examination in patients exhibiting strong clinical and laboratory indicators of insulinoma, even when conventional imaging results are negative

KEYWORDS

Hypoglycemia, Insulinoma, Endoscopic Ultrasound, Fine Needle Aspiration Biopsy Technique.

INTRODUCTION

Insulinoma, a prevalent functional pancreatic neuroendocrine tumor (pNET), is characterized by specific insulin secretion, leading to endogenous hyperinsulinemia and subsequently resulting in hypoglycemia.[1] Insulinoma is the predominant cause of hypoglycemia related to endogenous hyperinsulinemia, which occurs in approximately 1 to 4 individuals per million.[2] The primary clinical manifestations of insulinoma include spontaneous hypoglycemia, psychiatric abnormalities, and neurological symptoms such as impaired consciousness and seizures.[3] While qualitative diagnosis of insulinoma is straightforward, the challenge lies in localizing the often small and hidden tumor. Some patients, despite traditional imaging, remain undiagnosed or are misdiagnosed. Herein, in this report, we present a case of insulinoma with an occult tumor and provide a comprehensive review of the relevant literature, aiming to raise awareness among clinicians regarding early diagnosis and treatment of insulinoma.

CASE HISTORY AND EXAMINATION

A 44-year-old female patient was admitted to our department on January 30, 2020, following recurrent syncope and profuse sweating over the past two years, with worsening symptoms in the last month. The patient experienced recurrent syncope accompanied by profuse sweating, without an obvious trigger, for

the past two years. These episodes primarily occurred in the early morning, but were alleviated by eating, with approximately one episode every six months. The patient denied any speech abnormalities or hemiplegia. Previously, the patient received treatment at a local hospital, where an intravenous random blood glucose measurement revealed a level of 54.72 mg/dL, indicating hypoglycemia. Imaging studies, including chest, abdominal, and cranial CT scans, revealed no abnormalities, and thus no additional treatment was administered.

The patient started undergoing frequent seizures approximately one month ago, occurring once a week. Accompanying these seizures, she experienced impaired consciousness and incoherent speech, with symptom relief after eating. The patient was admitted to the hospital for evaluation of syncope. Over the past two years, the patient's dietary intake had increased, resulting in a weight gain of approximately 5 kg. Her medical history included a cesarean-section hemorrhage, followed by regular menstruation after delivery. For the past five years, she had been dealing with hypertension, although her treatment adherence was inconsistent. There were no notable findings in her family medical history.

The patient's vital signs were stable during the physical examination. Her height measured 153 cm, weight 74 kg, with a BMI of 31.61 kg/m^2. The patient was alert and provided relevant answers. No signs of acanthosis nigricans or hyperpigmentation were observed on the skin or mucous membranes. Axillary and pubic hair appeared within normal limits. No enlargement of the thyroid gland was noted. Cardiopulmonary and abdominal examinations revealed no abnormalities. Muscle strength and tone in the extremities were within normal limits. No pathological signs were detected.

INVESTIGATIONS AND DIAGNOSIS

Upon experiencing dizziness and palpitations following admission, intravenous blood glucose measured 32.58 mg/dL, insulin level was 108.7 mIU/L, and the insulin release index (IRI/G) was calculated as 3.32. The results of the glucose tolerance test, C-peptide measurement, and insulin release test are presented in Table 1. Abnormal findings included blood tests, liver and kidney function, glycosylated hemoglobin levels, tumor markers, adrenocorticotropic hormone, cortisol, thyroid function, parathyroid hormone, growth hormone, and sex hormones. Thyroid function, parathyroid hormone, growth hormone, and sex hormone levels were within normal limits. Abdominal imaging revealed no abnormalities. Ultrasound endoscopy revealed a hypoechoic nodule in the pancreatic neck, measuring approximately 11.2 × 12.7 mm (Figure 1). Ultrasound endoscopy-guided puncture of the pancreatic nodule revealed pancreatic tissue strip lesions, characterized by epithelioid cells arranged in a nest-like pattern. Uniform cell size and cytoplasmic richness were noted. A neuroendocrine tumor was suspected (Figure 2 and Figure 3). Following transfer to general surgery department, post-abdominal exploration revealed an approximately 1 cm diameter nodule in the pancreatic neck (Figure 4). Intraoperative ultrasound confirmed a hyperechoic nodule in the same location. Pancreaticoduodenectomy was subsequently performed. The postoperative autopsy specimen revealed a well-defined mass, measuring 1.2 × 1.4 cm, located in the pancreatic neck (see Figure 5). The intraoperative rapid pathology report confirmed the presence of a neuroendocrine tumor. Postoperative histopathology demonstrated anisotropic cell proliferation within the pancreatic tissue, characterized by glandular duct-like and small nest-like structures(see Figure 6). The tumor cells exhibited uniformity and minimal heterogeneity, consistent with a neuroendocrine tumor.

Outcome and follow-up

Two weeks post-surgery, the patient exhibited elevated blood glucose levels. Fasting blood glucose measured 274.32 mg/dL, and 2-hour postprandial blood glucose was 334.26 mg/dL(see Table 2), indicating secondary diabetes mellitus. Insulin therapy was initiated for glycemic control. Following hospital discharge, the patient used insulin sporadically, without experiencing hypoglycemia. Six months post-surgery, fasting blood glucose was 284.58 mg/dL, and glycosylated hemoglobin was 12.5%. The patient received instructions to use insulin consistently. Over the subsequent four years, no hypoglycemic episodes occurred, and glycemic control remained reasonable.

Discussion

Insulinomas are commonly encountered as solitary benign tumors, typically measuring less than 2 cm in diameter, and they constitute 87% of all pancreatic tumors.[4] On the other hand, the malignant ones account for the remaining 13%. These malignant variants tend to be larger, with an average size of 6.2 cm. The most frequent locations for insulinomas are the tail, body, and head of the pancreas. Notably, they often coincide with a significant elevation in insulin levels. The five-year survival rates differ markedly between benign and malignant tumors, standing at 95.4% and 66.8%, respectively. [5] Approximately 4% to 7% of insulinomas are associated with multiple endocrine neoplasia type-1 (MEN-1), a condition characterized by an earlier age of onset and multifocality. [6] Despite extensive research, the etiology and pathogenesis of insulinomas remain elusive. Clinically, the patients with an insulinoma manifest primarily as episodic hypoglycemia, primarily due to excessive insulin secretion from the tumor tissue. The diagnostic criteria for insulinoma include the Whipple's triad sign: (1) spontaneous periodic episodes of hypoglycemic symptoms, coma, and associated psychoneurological symptoms, often occurring during fasting or after physical exertion; (2) blood glucose levels below 50.4 mg/dL during these episodes; and (3) prompt resolution of the symptoms following oral or intravenous glucose administration. In cases with atypical clinical manifestations, a 72-hour starvation test is essential for a definitive diagnosis. [7, 8] The symptoms and the test results of the patient in our reported case meet the qualitative diagnostic criteria for insulinoma.

Benign insulinomas commonly respond well to surgical resection, and we now have a variety of alternative therapeutic options. These include endoscopic ultrasound-guided radiofrequency ablation, percutaneous alcohol ablation, and transarterial embolization of the insulinoma.[9, 10] The preoperative localization of insulinomas directly impacts the clearance rate, reoperation rate, and prognosis of the lesion. Accurate localization diagnosis remains a significant challenge in insulinoma diagnosis and treatment. Advancements in imaging technology have ushered in an era of simple and non-invasive preoperative localization and diagnosis of insulinomas. Invasive techniques, such as digital subtraction angiography, percutaneous hepatic portal vein blood sampling, and selective arterial calcium-stimulated venous blood collection, have fallen out of favor. Routine imaging modalities, including ultrasound of the upper abdomen, Magnetic Resonance Imaging (MRI), Contrast-Enhanced Computed Tomography (CECT) of the abdomen, and pancreatic CT perfusion imaging, are widely employed for localization and diagnosis. In a single-center study, 286 patients with functional pancreatic neuroendocrine tumors (pNETs) were included, of whom 266 had insulinomas. The study demonstrated that CT, DSA, ultrasonography, and MRI achieved favorable localization and diagnostic rates of 76.2%, 83.8%, 87.1%, and 92.9%, respectively.[11] Computed tomography (CT) and magnetic resonance imaging (MRI) serve as primary imaging modalities for localization and diagnosis of insulinomas. However, their sensitivity remains inadequate, particularly for small-volume lesions. Improving the detection rate and addressing deficiencies in lesion characterization are ongoing challenges. Emerging imaging techniques, including 68Gallium-DOTA-Tyr3-Octreotate Positron Emission Tomography-Computed Tomography (68Ga-DOTATATE-PET-CT) and 68Gallium-NOTA-exendin-4 Positron Emission Tomography-Computed Tomography (68Ga-NOTAexendin-4PET-CT), and other radionuclide receptor imaging tests, exploit receptor-binding based imaging for precise localization. In a prospective study, 68Ga-DOTATATE-PET-CT demonstrated superior sensitivity for lesion detection and tumor-staging guiding, compared to whole-body diffusion-weighted MRI (WB DWI) and 99mTc-HYNIC-Octreotide SPECT/CT. Diagnostic performance metrics for pancreatic neuroendocrine tumors were as follows: sensitivity 100%, specificity 80%, accuracy 84%, positive predictive value 57%, and negative predictive value 100%.[12] Despite their clinical significance, wider adoption of these novel imaging tests remains limited due to availability constraints in many hospitals. In this case, abdominal enhancement CT failed to detect the lesion, and radionuclide receptor imaging was not performed. Hence, alternative localization methods are necessary for further clarification.

Given that surgical removal of the tumor remains the sole effective treatment, to prevent undue harm to the patient resulting from misdiagnosis, a preoperative "gold standard" diagnosis is imperative, which necessitates the pathologic examination. Endoscopic ultrasound (EUS) offers the advantages of high resolution, proximity, and minimal interference from intestinal gas. During both preoperative and intraoperative phases, it allows comprehensive observation of the lesion from all angles, eliminating blind spots and facilitating precise tumor localization. In comparison to alternative imaging modalities, endoscopic ultrasound offers

notable benefits, particularly in enhancing the detection rate of small lesions. Additionally, it can be used in conjunction with fine-needle aspiration biopsy to perform histologic and cytologic examinations on the lesion. Furthermore, it enables qualitative diagnosis of the lesion, informing treatment decisions. In situations where conventional imaging results are inconclusive, it serves as a crucial complementary tool.[13]

However, EUS as an invasive procedure has several drawbacks. The diagnostic effectiveness of insulinomas via EUS is constrained by the location and size of the tumors. Specifically, EUS is less effective in detecting insulinomas situated in the tail or the leptomeningeal region of the pancreas, both of which tend to be small. The reliability of EUS depends on the subjective interpretation of the sonographer, introducing limitations. Detecting isoechoic insulinomas poses challenges for EUS, and it cannot identify extra-pancreatic lesions like lymph node or liver metastases. In this case, the patient underwent the EUS examination, and a small lesion in the pancreatic neck, a location prone to oversight, was identified. The fine-needle aspiration biopsy was subsequently conducted to ascertain the lesion's nature, confirming it as a neuroendocrine tumor. The precise diagnosis of the lesion's location and nature enabled the patient to proceed with the next stage of surgical treatment.

After pancreaticoduodenectomy, the patient did not encounter hypoglycemic episodes. Hyperglycemia was attributed to secondary diabetes mellitus. Exogenous insulin treatment resulted in adequate glycemic control. Postoperatively, the patient underwent follow-up, with no evidence of recurrence or metastasis.

The EUS-guided fine-needle aspiration biopsy (EUS-FNAB) serves as a critical adjunctive technique when conventional imaging fails to precisely localize and diagnose occult insulinomas. Furthermore, novel molecular imaging technologies, including 68Ga-DOTATATE-PET-CT and 68Ga-NOTAexendin-4PET-CT, also offer precise and reliable localization of the tumors. These advancements enhance clinicians' diagnostic and therapeutic capabilities for occult insulinomas, minimizing misdiagnoses and enabling early intervention.

Author Contributions

Yuhua Chen:Conceptualization,Zhongqiu Guo:Writing- Original draft preparation,RonghuoLiu:Validation,Yanrong Chan:Writing- Reviewing and Editing

Ethics Statement

The data for this case report were taken from the case clinical records and anonymized. Written patient consent was gained for this case report

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Table1 Glucose tolerance test, C-peptide and insulin release tests

	0min	30min	60min	120min	180min	240min	300min
blood glucose(mg/dl)	58.32	174.24	218.70	188.10	102.24	60.66	37.62
Insulin(ulu/ml)	49.43	108.8	147.6	76.81	46.66	41.38	53.32
C-peptide(ng/ml)	6.68	12.61	17.06	12.54	9.13	7.50	8.13
Insulin release index	0.84	0.62	0.67	0.41	0.46	0.68	1.42

Table2 Postoperative glucose, insulin and C-peptide changes

	fasting blood glucose (mg/dl)	2-hour postprandial glucose(mg/dl)	fasting insulin(ulu/ml)
Two weeks postoperative	274.32	334.26	7.07
Six Months Post-Operative	284.58	-	4.76

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`Table1 Glucose tolerance test.docx` available at https://authorea.com/users/821533/articles/1219487-the-occult-insulinoma-was-localized-using-endoscopic-ultrasound-guidance-a-case-report

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