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Case Report
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Unexplained Hypoglycemia in a Diabetic Patient: Unveiling Insulinoma

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ABSTRACT

Background: Insulinomas are rare, typically benign, insulin-secreting neuroendocrine tumors with an incidence of 1–32 cases per million annually. They commonly present with Whipple's triad: symptoms of hypoglycemia, low plasma glucose, and resolution of symptoms with glucose administration. The coexistence of insulinoma with type 2 Diabetes mellitus (T2DM) is highly uncommon and often results in diagnostic delays due to overlapping clinical features and misattribution of hypoglycemia to hypoglycemic agent therapy.

Case Presentation: We describe a case of a 65-year-old lady with a 16-year history of T2DM and hypertension. The patient presented with persistent symptomatic hypoglycemic episodes despite discontinuation of insulin therapy. Her HbA1c ranged between 5.7% and 8.4% over the past year. She was previously managed with 40 units/day of premixed insulin. Hypoglycemic episodes continued after insulin cessation, prompting inpatient evaluation. During hospitalization, the plasma glucose was recorded at 33 mg/dL with concurrent inappropriately elevated insulin levels (74.4 µIU/mL) and C-peptide (8.5 ng/mL) levels, confirming an endogenous hyperinsulinemia. These laboratory results prompted further evaluation to conclude endogenous hyperinsulinemia. Chromogranin A was markedly elevated (350 ng/mL). Imaging via contrast-enhanced CT scan revealed a 14-mm hyper-vascular lesion in the pancreatic tail. The patient underwent a successful laparoscopic distal pancreatectomy. Histopathology confirmed a 17-mm, well-differentiated, grade 3 pancreatic neuroendocrine tumor, positive for chromogranin A and synaptophysin. Postoperatively, she developed persistent hyperglycemia requiring resumption of premixed insulin at 0.6 U/kg/day. At 3-month follow-up, she remained insulin-dependent but was free of further hypoglycemic episodes.

Discussion: This case underscores the diagnostic complexity when insulinoma coexists with long-standing T2DM. In patients with continued hypoglycemia after insulin withdrawal, endogenous causes such as insulinoma must be considered. Insulinoma, though uncommon, is a neuroendocrine tumor. High clinical suspicion, biochemical profiling during hypoglycemic episodes, and timely imaging are essential for the diagnosis of Insulinoma. Notably, this case involved a well-differentiated grade 3 tumor; an uncommon histological finding in insulinomas, which may have implications for surveillance due to its potential for

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more aggressive behavior. Atypical histological findings should prompt the clinician to investigate for other neuroendocrine tumors in the body, which might be associated with a syndrome group. The persistence of diabetes post-resection highlights the ongoing insulin resistance related to long-standing T2DM, despite tumor removal. This case is unique in the sense that this neuroendocrine tumor is not associated with a syndrome group but presents with unusual histological findings.

Conclusion: Insulinoma should remain a differential diagnosis in diabetic patients presenting with unexplained or worsening hypoglycemia, particularly after insulin withdrawal. Early diagnosis, appropriate imaging, and surgical resection are crucial for favorable outcomes. Postoperative metabolic monitoring remains essential due to the dual risk of hyperglycemia due to long-standing insulin resistance and hypoglycemia.

KEYWORDS: *insulinoma, type 2 diabetes mellitus, neuroendocrine tumor, hypoglycemia, endogenous hyperinsulinemia, pancreatic tumor, grade 3 NET, surgical resection*

INTRODUCTION

Insulinomas are rare, insulin-secreting neuroendocrine tumors of the pancreas that lead to recurrent episodes of hypoglycemia (1). The condition has an estimated annual incidence of 1 to 32 cases per million individuals. Insulinomas are known to have a slight female preponderance. These tumors are typically benign, solitary, and sporadic (1). A small percentage, however, are associated with multiple endocrine neoplasia type 1 (MEN1), which often presents at a younger age with numerous tumors (1). Clinically, insulinomas present with Whipple's triad: hypoglycemic symptoms, documented low plasma glucose, and resolution of symptoms after glucose administration (2). Although fasting hypoglycemia is the most common presentation, postprandial hypoglycemia has also been reported, though less frequently (2). Epidemiological studies show a consistently low global incidence of insulinoma, though regional variation exists. Higher incidence of Insulinomas are seen in Scandinavian countries. Although the incidence of the neuroendocrine tumor is rare, it is one of the most common functional pancreatic neuroendocrine tumors.

The coexistence of insulinoma and type 2 diabetes mellitus (T2DM) is rare (4). In such cases, the excess insulin from the tumor may initially improve glycemic control or cause unexpected hypoglycemia, leading to confusion in clinical assessment (4). As a result, symptoms are often misattributed to diabetes treatment rather than an underlying tumor, delaying diagnosis (3). Biochemical diagnosis relies on measuring insulin, C-peptide, and glucose levels during a spontaneous or provoked hypoglycemic episode, followed by localization through imaging modalities such as CT, MRI, or endoscopic ultrasound (1). Surgical resection remains the standard treatment for localized insulinomas, with most solitary tumors being successfully cured through surgery (4). Enucleation is preferred for small, benign tumors away from the central pancreatic duct, whereas larger or deeper tumors usually require a distal pancreatectomy (4). With the increasing use of minimally invasive techniques and intraoperative ultrasound, both tumor localization and patient recovery have significantly improved (4).

This case report discusses a 65-year-old Indian woman with a history of T2DM who presented with recurrent hypoglycemic episodes and was ultimately diagnosed with insulinoma. The case highlights the diagnostic challenges of this unusual coexistence and emphasizes the need to consider insulinoma in diabetic patients presenting with atypical or unexplained hypoglycemia.

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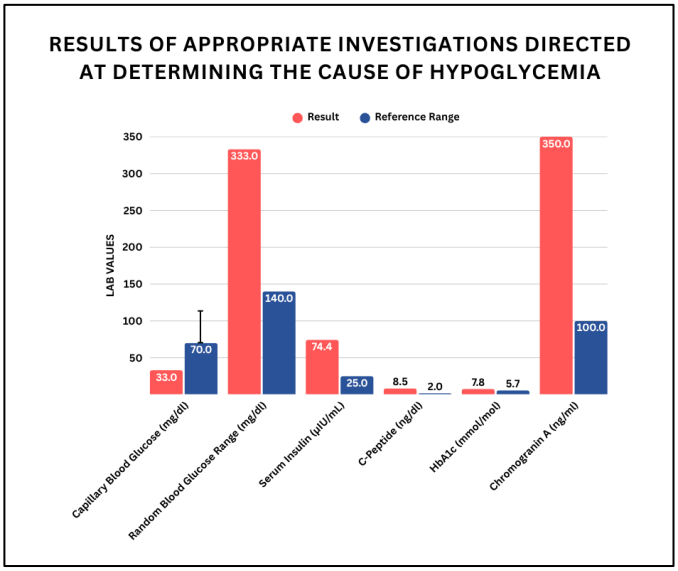
CASE PRESENTATION

A 65-year-old obese lady (with a 16-year history of type 2 diabetes mellitus (T2DM) and hypertension) presented to our outpatient clinic with complaints of recurrent hypoglycemic episodes. She had been on multiple daily injections of premixed insulin totaling 40 units/day (0.5 U/kg) and reported no use of other hypoglycemic agents. Her glycated hemoglobin (HbA1c) had ranged between 5.7% and 8.4% (49–68 mmol/mol) over the last year. There was no history of long-term diabetic complications or significant family history of diabetes or endocrine disorders. Approximately six months ago, she began experiencing frequent symptoms, including fatigue, blurred vision, disorientation, and weakness, symptoms that resolved with food intake. Home glucometer readings consistently confirmed hypoglycemia, despite gradual reduction and eventual cessation of insulin therapy five weeks before her hospital visit. However, hypoglycemic episodes persisted even after insulin cessation, prompting hospital admission.

At the time of admission, the patient had a five-week abstinence from exogenous insulin administration, she had gained 3 kg in weight, and her HbA1c was 7.8%. During hospitalization, her random blood glucose readings fluctuated in the range of 44 to 333 mg/dL, despite taking regular meals. During a documented symptomatic episode, capillary blood glucose was 33 mg/dL. Further evaluation revealed inappropriately elevated serum insulin (74.4 µIU/mL) and C-peptide levels (8.5 ng/mL), measured using the ECLIA method, confirming a state of endogenous hyperinsulinemia. Chromogranin A was markedly raised at 350 ng/mL (normal <100 ng/mL), indicating a neuroendocrine origin (Figure 1). Additional lab workup showed normal renal and liver function, and endocrine evaluation ruled out adrenal insufficiency and hypothyroidism. Although a sulfonylurea screen was not performed due to unavailability, covert ingestion of oral hypoglycemic agents was considered highly unlikely, as the patient had no prior exposure, unavailability of large quantities of oral hypoglycemic agents, no family history of diabetes, and no pharmacy record suggesting its use. Alternative laboratory investigations that can be done include serum electrolytes (serum potassium levels) to rule out the possibility of exogenous insulin administration, a urine toxicology screen to eliminate the possibility of consumption of oral hypoglycemic agents.

Figure 1: Results of appropriate investigations directed at determining the cause of hypoglycemia.



Contrast-enhanced abdominal CT scan revealed a 14-mm hypervascular lesion in the tail of the pancreas, raising the suspicion of insulinoma. There were no features suggestive of multiple endocrine neoplasia type 1 (MEN-1). The patient underwent laparoscopic distal pancreatectomy, and histopathology confirmed a 17-mm well-differentiated grade 3 pancreatic neuroendocrine tumor, positive for chromogranin and synaptophysin on immunostaining, consistent with insulinoma. Following surgery, the patient developed persistent hyperglycemia, requiring resumption of premixed insulin therapy at 40 units/day (0.6 U/kg). At three months postoperatively, she remained insulin-dependent with an HbA1c of 8.3% (67 mmol/mol) but was free from any further hypoglycemic episodes.

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DISCUSSION

Insulinoma occurring together with T2DM is a rare and challenging case for clinicians to diagnose. Although Insulinomas are a common type of neuroendocrine tumors, it is scarce for these tumors to appear in those with existing T2DM. An advanced degree of suspicion is required to promptly arrive at a conclusive diagnosis of Insulinoma, in a patient who was managed for hyperglycemia, they mistake a severe low blood glucose level for a regular hypoglycemic event that is common with T2DM management (5).

This 65-year-old patient with a long history of T2DM continued to have hypoglycemia despite not taking insulin. Noticing that the patient kept having hypoglycemia even without insulin prompted a targeted endocrine evaluation. Having high insulin and C-peptide during hypoglycemia indicated that the patient had an insulinoma (6).

Further difficulties arise because the symptoms of hypoglycemia, such as feeling tired and confused, can be confused with typical symptoms of uncontrolled diabetes or its problems. Such symptoms can be linked to fluctuations in blood glucose, faulty administration of medications, or even diabetic neuropathy involving the autonomic nervous system(7). Because of this, it is important to be suspicious, especially when someone continues to have hypoglycemia after changing or stopping their insulin treatment.

Tumor localization before surgery depends greatly on imaging. In our situation, the contrast-enhanced CT scan discovered a highly vascular tumor in the tail of the pancreas. Although CT and MRI are highly sensitive for revealing tumors that are larger than 1 cm, small insulinomas may remain undetected. In challenging cases, more precise methods such as EUS and PET/CT are being used to increase the accuracy of the diagnosis(8).

The histopathological finding showed that this insulinoma is a well-differentiated grade 3 neuroendocrine tumor (NET), which is quite unusual. Most insulinomas have grade 1 or 2 and remain benign; however, a few NETs with grade 3 can behave more aggressively despite being very differentiated. Being based on both mitotic count and the Ki-67 index, the 2022 WHO classification supports accurate predictions and the planning of treatment and surveillance measures (9). The Ki-67 index is divided into three categories: G1,G2, and G3, depending upon the cell proliferation rate in the tumor. A higher Ki-67 grade correlates to an advanced tumor.

After surgery, the outcome was noticeable: glucose levels rose to normal, but insulin had to be started again since hyperglycemia returned. It means that even after tumor removal, the insulin resistance that comes with long-term T2DM will not be cured. Because the tumor's insulin production is no longer present after treatment, physicians should anticipate needing more insulin for their patients' diabetes.

This case shows the importance of considering the possibility of insulinoma in people with diabetes who have unexplained or increasing hypoglycemia, especially after they stop using insulin. Removing the tumor at an early stage and performing surgery is the main way to offer a cure. Additionally, this case demonstrates the necessity of tailored postoperative metabolic monitoring, as the risks of high and low blood sugars can increase significantly.

CONCLUSION

The case describes a patient with long-term type 2 diabetes mellitus who ended up with insulinoma, pointing out that both conditions sometimes show similar symptoms. If hypoglycemia continues even with no insulin, exploring for endogenous hyperinsulinism, perhaps caused by insulinoma, should be considered in diabetic patients as well. Although surgery is still the primary choice, managing diabetes after surgery may be difficult due to long-standing type 2 diabetes mellitus, which results in persistent insulin resistance and dysfunction of Pancreatic islet beta cells, prompting

resumption of exogenous insulin administration. Knowing about this rare disease allows for early identification and suitable treatment, leading to better patient results. This case aims to highlight the consideration of performing a sulfonyl urea screen, a urine toxicology screen while treating atypical presentation of hypoglycemic episodes in a patient with long-standing type 2 diabetes mellitus to elicit a superior quality of treatment and diagnosis.

Informed Consent

The patient granted permission via written consent for his anonymous details to be published in this research article.

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Conflict of Interest Statement

The authors confirm that there is no conflict of interest related to this project.