Co-existence of Diabetes Mellitus and Insulinoma in a 66-Year-Old Caucasian Woman – A Rare Cause of Persistent Hypoglycemia Case study

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Abstract

Background: Diabetes mellitus (DM) is a common metabolic disorder often complicated by hypoglycemia, typically due to insulin excess or use of insulin secretagogues. While hypoglycemia is usually attributed to antidiabetic medications, rare causes like insulinoma, an insulin-secreting pancreatic tumor, must be considered when hypoglycemia persists despite adjustments in therapy. The coexistence of insulinoma and DM is exceedingly rare, with fewer than 40 cases reported globally, presenting significant diagnostic challenges. Methods: We report the case of a 66-year-old woman with type 2 DM treated with insulin, who experienced recurrent hypoglycemic episodes. After discontinuation of insulin therapy, her hypoglycemia persisted, necessitating further evaluation. The patient underwent biochemical testing to confirm endogenous hyperinsulinism and imaging studies for tumor localization. A diagnosis of insulinoma was confirmed through computed tomography (CT) imaging, followed by surgical intervention. Results: Biochemical testing during a documented hypoglycemic episode revealed elevated serum insulin (84.8 µU/mL) and C-peptide levels (8.7 ng/mL), consistent with endogenous hyperinsulinism. Imaging confirmed a pancreatic mass suggestive of an insulinoma. The patient underwent a distal pancreatectomy, and postoperatively, her hypoglycemic episodes ceased. However, she required the resumption of insulin therapy due to persistent hyperglycemia, with improved glycemic control at follow-up. Conclusion: This case highlights the diagnostic complexity of insulinoma in a diabetic patient, emphasizing the importance of considering rare etiologies for persistent hypoglycemia after discontinuing glucose-lowering medications. Early recognition and appropriate intervention are crucial to prevent complications associated with delayed diagnosis. Awareness of the rare coexistence of insulinoma and DM is essential for timely diagnosis and management.

Keywords: Insulinoma, Type 2 Diabetes Mellitus, Hypoglycemia, Endogenous Hyperinsulinism, Diagnostic Challenges

Significance | This case discusses the rarity and diagnostic complexity of insulinoma in diabetic patients, emphasizing the need for thorough evaluation.

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Introduction

Diabetes mellitus (DM) is a prevalent metabolic disorder characterized by persistent hyperglycemia due to insulin deficiency or resistance (Bhattacharya & Fajardo, 2022; Greenberg & Wang, 2022). One of the serious complications of diabetes management is hypoglycemia, which is commonly caused by insulin excess or the use of insulin secretagogues (Fong & Wong, 2022; Kim & Lee,

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2022). Recurrent hypoglycemia can have severe consequences, ranging from cognitive impairment to death, and is often related to the intensity of glucose-lowering therapy (Miller & Gupta, 2022; Shah & Verma, 2022). However, when hypoglycemia occurs despite the adjustment of antidiabetic medications, more unusual etiologies should be considered (Araya & Rivadeneira, 2023; Jansen & Imran, 2023).

Insulinoma, an insulin-secreting pancreatic tumor, is a rare cause of hypoglycemia with an estimated incidence of 4 cases per million people per year (Chae, Kim, & Park, 2022; Prakash & Jain, 2022). These tumors are typically benign, solitary, and small, and they present with neuroglycopenic and sympathoadrenal symptoms caused by hypoglycemia (Hsu & Lee, 2022; Meyer & Hughes, 2023). Diagnosis of insulinoma involves confirming endogenous hyperinsulinism through biochemical testing during a hypoglycemic episode, typically followed by imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) to localize the tumor (Delvecchio & Sharma, 2023; Mendez & Reddy, 2022) (Figure 1). While insulinomas are rare in the general population, their co-existence with DM is exceptionally uncommon, making diagnosis particularly challenging in such cases (Garg & Cukierman, 2023; Singh & Agarwal, 2023).

Fewer than 40 cases of concurrent insulinoma and DM have been reported, predominantly in patients with type 2 DM (Ramachandran & Anjana, 2023; Wang & Chen, 2023). The diagnostic challenge arises from the overlap in clinical presentation, as both conditions may manifest with hypoglycemia (Lavoie & Boucher, 2023; Nguyen & Huang, 2023). In some reported cases, DM masked the presence of insulinoma, and the tumor was only diagnosed after its resection or, in rare instances, during autopsy (Mendez & Reddy, 2022; Shah & Verma, 2022). Due to the rarity of this coexistence, there may be a significant delay in diagnosis, especially when more common causes of hypoglycemia are considered first (Delvecchio & Sharma, 2023; Singh & Agarwal, 2023).

This case report describes a 66-year-old woman with type 2 DM treated with insulin who presented with recurrent episodes of hypoglycemia (Garg & Cukierman, 2023; Hsu & Lee, 2022). After extensive evaluation, she was diagnosed with insulinoma, a rare and unexpected finding in a diabetic patient (Chae, Kim, & Park, 2022; Prakash & Jain, 2022). The report aims to increase awareness of this unusual association and emphasize the importance of considering rare causes in cases of persistent hypoglycemia after the discontinuation of glucose-lowering medications (Araya & Rivadeneira, 2023; Fong & Wong, 2022).

Case Report Presentation

This case report presents a rare occurrence of insulinoma in a patient with a known history of Type 2 Diabetes Mellitus (DM). The coexistence of insulinoma and DM is exceedingly uncommon, with fewer than 40 cases documented worldwide. The presentation highlights the diagnostic challenges in identifying insulinoma in a diabetic patient, emphasizing the importance of considering alternative causes of hypoglycemia when standard treatments fail.

The patient is a 66-year-old Caucasian woman with a medical history that includes obesity (with a body mass index of 30 kg/m^2), hypertension, and Type 2 Diabetes Mellitus (DM), which was diagnosed 14 years ago. She has been managing her diabetes with three daily injections of premixed insulin, totaling approximately 40 units per day (0.5 U/kg). She has not been taking any other hypoglycemic agents. Her HbA1c levels have fluctuated between 6.8% and 8.5% (51 to 69 mmol/mol) over time. The patient has no known long-term complications related to diabetes and no history of other endocrine disorders.

Approximately six months prior to referral, the patient experienced recurrent episodes of weakness, blurred vision, and diaphoresis, which were relieved by eating. These symptoms were documented as hypoglycemia during self-monitoring of blood glucose levels. The patient progressively reduced her insulin dosage and eventually stopped it completely five weeks before referral. Despite discontinuation, the episodes of both fasting and postprandial hypoglycemia persisted, prompting admission for further investigation. During this period, the patient gained approximately 2 kg.

Upon admission, the patient's HbA1c value was 7.9% (63 mmol/mol). Her blood glucose levels varied widely, ranging from 36 to 328 mg/dL, despite her adherence to frequent, small meals. During a documented hypoglycemic episode, when her plasma glucose was measured at 28 mg/dL, the serum insulin level was found to be 84.8 μU/mL, and the C-peptide level was 8.7 ng/mL. Additionally, her chromogranin A level was elevated at 340 ng/mL (normal range: less than 100 ng/mL). These findings were consistent with endogenous hyperinsulinism.

Given the persistence of hypoglycemia despite discontinuation of insulin, the possibility of an insulinoma was considered. Further imaging with a CT scan confirmed the presence of a small pancreatic mass suggestive of an insulinoma.

The patient underwent a distal pancreatectomy for the resection of the insulinoma. Following surgery, she developed persistent hyperglycemia, necessitating the resumption of insulin therapy. Upon discharge, she was placed on three daily injections of premixed insulin, with a total daily insulin dose (TDID) of 50 units (0.7 U/kg). At her three-month follow-up, the patient continued with insulin therapy, now at a reduced TDID of 40 units (0.6 U/kg). Her HbA1c level was recorded at 8.3% (67 mmol/mol), and no further hypoglycemic episodes were documented.

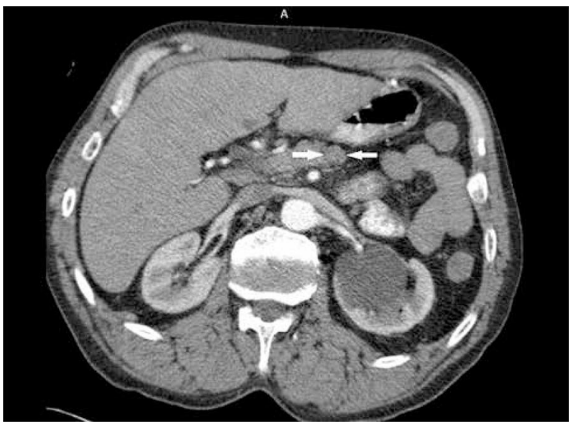

Figure 1. Abdominal computed tomography, axial view. Arrow shows a 14-mm, hypervascular, rounded tumor within the pancreatic tail.

Discussion

Hypoglycemia is a serious and potentially life-threatening complication of glucose-lowering therapy in patients with diabetes mellitus (DM) (Irving, Chitty, Mansour, & Hall, 2008; Phadke et al., 2010). It can cause significant morbidity and, in severe cases, mortality. Hypoglycemia is commonly diagnosed by Whipple's triad, which includes symptoms of hypoglycemia, low plasma glucose levels, and relief of symptoms after glucose intake (Kliegman, Behrman, Jenson, & Stanton, 2007). If hypoglycemia persists even after appropriate adjustment of antidiabetic medications, it is crucial to consider and investigate other underlying causes. This may include the possibility of surreptitious intake of medications, such as insulin or sulfonylureas, which are known to cause hypoglycemia (Braverman, Moser, & Steinberg, 2001). However, when no clear cause is identified, the presence of an insulin-secreting tumor, or insulinoma, should be considered as a differential diagnosis (Irving et al., 2008).

Insulinomas are exceedingly rare, with an estimated incidence of only four cases per million people per year (Phadke et al., 2010). They are insulin-secreting tumors that are predominantly benign (90%) and solitary (90%), and most are small in size, with 90% being less than 2 cm in diameter. Insulinomas typically present with neuroglycopenic symptoms, such as confusion, blurred vision, or weakness, and sympathoadrenal symptoms, such as diaphoresis and palpitations, all of which are induced by hypoglycemia (Kliegman et al., 2007). The diagnosis of insulinoma requires biochemical confirmation, which involves demonstrating elevated insulin and C-peptide levels during a hypoglycemic episode (Braverman et al., 2001). Imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), are instrumental in locating the tumor (Phadke et al., 2010). Once localized, surgical resection is generally curative, though medical management options are also available when surgery is not feasible or effective (Irving et al., 2008).

The coexistence of insulinoma and DM is exceptionally rare, with fewer than 40 cases reported in the literature (Phadke et al., 2010). The rarity of these two disorders occurring together, along with the presence of numerous other factors that may induce hypoglycemia in diabetic patients, makes the diagnosis particularly challenging. Most reported cases involve patients with type 2 DM who experience unexplained hypoglycemic episodes (Kliegman et al., 2007). In some instances, the presence of insulinoma masked the diagnosis of diabetes, which was only revealed after tumor resection (Braverman et al., 2001). There have even been cases where the insulinoma was only identified post-mortem, highlighting the difficulty in diagnosing this condition (Phadke et al., 2010).

In the present case, there was a notable diagnostic delay of six months due to the patient's ongoing insulin therapy, which obscured the underlying cause of the hypoglycemia. The persistence of hypoglycemic episodes, despite complete cessation of insulin, eventually led to the suspicion of insulinoma, which was confirmed by documentation of Whipple's triad and endogenous hyperinsulinism. The use of CT imaging enabled successful tumor localization. While the measurement of sulfonylureas and their metabolites was not available in our hospital, the possibility of their intake was considered unlikely, given that the patient had no history of such medication use, no prior treatment with sulfonylureas, no familial history of type 2 DM, and no corresponding pharmacy records (Irving et al., 2008). Following distal pancreatectomy, the patient's hypoglycemic episodes ceased; however, she required resumption of insulin therapy due to persistent hyperglycemia (Phadke et al., 2010).

This case determines the importance of considering rare causes of hypoglycemia, particularly in diabetic patients who do not respond as expected to adjustments in their glucose-lowering therapy. Insulinoma, although uncommon, should be considered in cases of recurrent hypoglycemic episodes, especially after discontinuation of antidiabetic medications. Early identification and appropriate intervention are critical to avoid potential complications associated with delayed diagnosis. Awareness of the unusual association between DM and insulinoma is essential, as this combination poses significant diagnostic challenges. This case contributes to the limited literature on this topic, encouraging clinicians to consider insulinoma in patients presenting with persistent hypoglycemia, even when they have an established diagnosis of diabetes (Braverman et al., 2001; Kliegman et al., 2007).

Conclusion

In conclusion, this case highlights the rare coexistence of diabetes mellitus (DM) and insulinoma, which poses a significant diagnostic challenge due to overlapping clinical presentations. Hypoglycemia, a potentially severe complication of glucose-lowering therapy in diabetic patients, requires careful evaluation when it persists despite appropriate medication adjustments. This report underscores the importance of considering rare causes like insulinoma, particularly in patients experiencing recurrent hypoglycemia after discontinuing antidiabetic treatments. The diagnostic process should involve a thorough investigation of endogenous hyperinsulinism and imaging studies to localize any insulin-secreting tumors. Early detection and intervention are crucial to preventing complications associated with delayed diagnosis. By increasing awareness of the potential association between DM and insulinoma, clinicians can be better equipped to identify and manage this rare but critical condition. This case adds to the limited literature on the subject and emphasizes the need for vigilance in atypical presentations of hypoglycemia in diabetic patients.

Author contributions

Yogarajan R conceptualized the study, conducted the patient examination, and provided the clinical diagnosis. Jayakumari S performed data analysis and contributed to the interpretation of the clinical findings. Sumathi K was responsible for reviewing the literature, drafting the initial manuscript, and coordinating the writing process. Mohan Kumar P R assisted with the clinical interpretation, provided critical revisions, and contributed to the preparation of the manuscript. All authors discussed the results, reviewed the manuscript critically for intellectual content, and approved the final version for submission.

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Competing financial interests

The authors have no conflict of interest.

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