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Persistent Hypoglycemia: a Rare Case Report of Clinically Diagnosed Insulinoma

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ABSTRACT
Insulinoma is a rare disease, with an incidence of approximately 4 cases per 1 million people per year. It is a pancreatic tumor that produces insulin and is classified as one of the functional pancreatic neuroendocrine tumors, originating from the pancreatic ductal cells. In insulinoma, insulin is produced abnormally and continuously, leading to persistent hypoglycemia due to excessive insulin levels. We report a case of a 49-year-old female patient who presented to the emergency department with a chief complaint of generalized weakness. The weakness was persistent and typically occurred before meals, improving after the consumption of sugar water. The patient also reported dizziness, cold sweats, blurred vision, and tremors. Laboratory tests revealed a random blood glucose level of 35 mg/dL, a fasting insulin level of 82.4 µIU/mL, and a C-peptide level of 1.07 ng/mL. Abdominal CT scan did not detect a pancreatic mass, and MRI findings were also inconclusive. Therefore, further evaluation with Endoscopic Ultrasound (EUS) and GLP-1R PET/CT was recommended. The diagnosis of insulinoma was made based on clinical and biochemical findings, fulfilling Whipple's triad and the diagnostic criteria of blood glucose < 55 mg/dL, insulin ≥ 55 µIU/mL, and C-peptide ≥ 0.6 ng/mL. The therapeutic algorithm for clinically and biochemically confirmed insulinoma includes stabilization of hypoglycemia, evaluation of tumor resectability, and administration of medical therapies such as everolimus, peptide receptor radionuclide therapy (PRRT) with Lu-177, chemotherapy, and local ablation techniques in cases of refractory disease

Keywords: Hipoglichemy, Whipple's triad, Insulinoma

Introduction

Insulinoma is the most common cause of endogenous hyperinsulinism, with an incidence of 1–4 per 1 million population per year (Rychlewska-Duda et al., 2025). There are 5% to 10% of cases that are malignant conditions (Yanitra & Martinus, 2023). Insulinoma is a neuroendocrine tumor of the pancreas that causes a variety of symptoms resulting from neuroglycopenic and autonomic stress responses to hypoglycemia. Insulinoma is a rare disease characterized by non-specific symptoms, and most patients are misdiagnosed and symptomatic for a prolonged period (Agbozo, 2023). Physiologically, the secretion of insulin by pancreatic beta cells is triggered when blood sugar levels are high. However, in insulinoma, insulin secretion continues even though blood sugar levels are low. Two signaling pathways play a role in

insulinoma tumorigenesis, namely a decrease in the activity of serine/threonine kinase p70S6K and an increase in the expression of phosphorylated mechanistic target of rapamycin (p-mTOR).

In 1935, Whipple and Frantz created a guideline for the diagnosis of insulinoma known as Whipple's triad, which consists of hypoglycemia (blood sugar levels <50 mg/dl), neuroglycopenic symptoms, and symptom improvement after glucose administration. The clinical manifestations of hypoglycemia include palpitations, cold sweats, and tremulousness. Meanwhile, severe hypoglycemia symptoms can trigger a neuroglycopenic state characterized by blurred vision, foggy consciousness, seizures, behavioral changes, and amnesia. Patients will also experience weight gain because they tend to eat more frequently (Yanitra & Martinus, 2023).

Diagnostic confirmation of insulinoma is initially carried out based on blood marker analysis, namely an increase in insulin, proinsulin, and C-peptide levels along with a decrease in blood glucose levels, followed by non-invasive imaging such as contrast-enhanced CT scan, MRI, and PET/CT. If non-invasive imaging fails, it is followed by invasive imaging examinations such as Endoscopic Ultrasonography (EUS) and biopsy. Management of insulinoma includes curative surgery and the use of diazoxide or somatostatin (Yu et al., 2021; Hacisahi et al., 2024).

The purpose of this study is to report clinically and biochemically diagnosed cases of insulinoma, as well as to describe challenges in diagnosis and management in health facilities with limited resources. The research benefits include: (1) improving clinician understanding of the diagnostic approach to insulinoma, especially in cases with negative imaging results; (2) providing an overview of interim therapy strategies before definitive management; and (3) highlighting the importance of referrals to health centers with comprehensive facilities (such as EUS or PET/CT) for confirmation of tumor location. This report is expected to serve as a reference for handling similar cases, especially in resource-limited areas.

Case Reports

A 49-year-old woman came to the emergency room of Arifin Achmad Hospital with complaints of weakness since 4 days of SMRS. Drowning is felt constantly. Weakness is felt before eating. Weakness is reduced if the patient consumes sugar water. Patients also complain of stinginess, cold sweats, trembling and blurred vision. Complaints of foggy awareness, seizures and behavior changes are denied. The patient's appetite increased and he increased his weight from 80 kg to 85 kg in the last 4 months. The patient was a referral from Puri Husada Hospital and obtained the results of a CT Scan without Contrast there was a mass impression on the pancreatic caput ec susp. Malignancy, so the patient was referred to Arifin Achmad Hospital. In the last 2 years, patients have experienced complaints of weakness all over the body accompanied by cold sweats, drowsiness with blood glucose in the range of 30-50 mg/dL and routinely admitted to the emergency room of Puri Husada Hospital. The patient had no history of diabetes mellitus but the patient's mother had a history of diabetes mellitus. There is no history of violence in the family.

The patient appears moderately ill with cooperative compositional awareness. Blood pressure 148/71 mmHg, pulse 88x per minute, respiratory rate 20x per minute, temperature 36.7 C, TB 165 cm, BB 85 kg with BMI 31 (level II obesity). On physical examination there were no abnormalities. Laboratory examination found Hb 13.8 g/dL, Leukocytes 12,810 uL, Platelets 294,000 uL, Erythrocytes 5,170,000 uL, Hematocrit 43.7%, MCH 26.7 pg, MCV 84.5 fL, MCHC 31.6 g/dL, GDS 35 mg/dL, Na+ 137 mmol/L, K+ 3.0 mmol/L, Chloride 108 mmol/L. Urea 32.0 mg/dL, Creatinine 0.82 mg/dL CA 199 12.01 U/mL, CEA 1.0 ng/mL, C-Peptide 1.07 ng/mL,

Fasting insulin 82.4 uIU/mL, Morning serum cortisol 1 ug/dl, CT scan of the abdomen without and with contrast obtained normal size, no picture of mass in the pancreas.
MRI with contrast was obtained in the caput, corpus and cauda appearing homogeneous. Flat surface with homogeneous parenchymal texture, no visible mass. There are no lesions that give pathological signals in the parenchymal or peripancreatic region. The pancreatic ductus does not widen. The conclusion is not clear the presence of a mass in the pancreas.

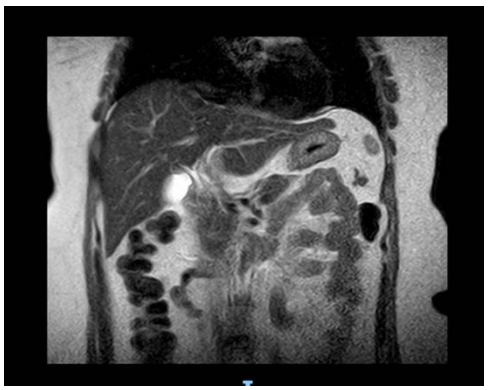

Figure 2. Abdominal MRI with contrast

Based on the anamnesis, physical examination and supporting examination of the patient were diagnosed as *Persistent Hypoglycemia et causa Clinically Diagnosed Insulinoma.* Patients received high-carbohydrate diet therapy 360 grams/day, D40% 2 flash (50 ml) intravenously and IVFD D10% 20 rpm, Hydrocortisone tab 2 x 40 mg po, Omeprazol caps 2 x 20 mg po.

Research Methods

This study uses *a case report* type of research to describe in detail clinical findings, diagnosis, and management in patients with insulinoma. The goal is to provide a comprehensive overview of the clinical presentation, diagnostic approaches, and therapies given in this rare case. Data was collected through an in-depth anamnesis to obtain a history of disease and symptoms, physical examinations to evaluate vital signs and clinical findings, and laboratory examinations such as blood glucose, insulin, C-peptide, and cortisol levels. In addition, imaging with CT scan and abdominal MRI was performed to identify lesions on the pancreas. The data source comes from the patient's medical records at Arifin Achmad Hospital, including laboratory results, radiology, and clinical records during treatment. Data analysis was carried out descriptively by comparing clinical and laboratory findings of patients with Whipple's triad diagnostic criteria and the latest management guidelines. Imaging results were assessed based on radiological consensus for pancreatic neuroendocrine tumors. With this approach, research is expected to contribute to the understanding and treatment of insulinoma cases that are difficult to diagnose.

Results and Discussion

Insulinoma is a neuroendocrine tumor of the pancreas, where it causes a variety of symptoms resulting from a neuroglycophenic and autonomic stress response to hypoglycemia. Hypoglycemia is a decrease in serum glucose concentrations with or without signs and symptoms of the autonomic system. The diagnosis guideline for insulinoma, known as Whipple's triad, is that there are symptoms of hypoglycemia, low blood glucose levels and symptoms that decrease with treatment.

In this case, a 49-year-old woman came in with reduced weakness with the administration of sugar, nausea, cold sweats, trembling and there was an additional neuroglycopenic symptom namely blurred vision. The initial GDS entered the emergency room at 35 mg/dL which indicates that the patient has severe hypoglycemia/level 3 according to the 2021 license book (Perkumpulan Endokrinologi Indonesia, 2021). In this patient, D40% 2 flc (50 ml) therapy was given IV and IVFD D 10% 20 rpm. This is in accordance with the protocol for managing severe hypoglycemia in the 2019 book guide. The purpose of giving D40% for Rapid correction of neuroglycopenia is to stop neurological symptoms and provide a rapid spike in plasma glucose levels of around 50-60 mg/dL (American Diabetes Association, 2023). Meanwhile, in the D10% infusion to maintain euglycemia after bolus and prevent hypoglycemia rebound, especially in patients with endogenous hyperinsulinemia such as insulinoma (Bhullar & Leung, 2020).

The clinical approach to insulinoma begins with the identification of persistent hypoglycemia symptoms due to intermittent insulin secretion by tumors, especially neuroglycophenic symptoms during fasting. The diagnosis was established through a 72-hour fasting glucose test which is a gold raw material, accompanied by an examination of glucose, insulin, C-peptide, and proinsulin levels during hypoglycemia. The results of the examination obtained in these patients were in the form of glucose < 55 mg/dL, insulin ≥ 55 μIU/mL, C-peptide ≥ 0.6 ng/mL which indicates hypoglycemic hyperinsulinemia typical in insulinoma (Nizam, 2025).

Most insulinoma patients have a normal CA value of 19-9 and in these patients they have a normal value of 12.01 U/mL with a normal value of <37 U/mL because CA 19-9 is only effective for detecting epithelial tumors such as pancreatic adenocarcinoma instead of neuroendocrine tumors (insulinoma) (Qian et al., 2022).

Other supporting tests such as CEA are tests that are considered non-specific and have low sensitivity in detecting insulinoma. In this patient, a CEA value of 1.0 ng/mL was obtained with a normal value of <3.0 (Rosiek et al., 2023).

Insulinoma is a functional pancreatic tumor that produces excessive insulin even when it is not needed, so the patient experiences recurrent hypoglycemia especially during fasting. When glucose levels drop, the body will increase counterregulatory hormones such as cortisol. Cortisol is secreted from the adrenal glands as part of the stress response to recurrent hypoglycemia. Evaluation of cortisol levels is very important in differential diagnosis of non-diabetic hypoglycemia. In this patient, the result of morning serum cortisol was 1 ug/dl, this can occur due to secondary functional hypocortisolism due to chronic hyperinsulinemia (Missaoui et al., 2025).

In this patient, Hydrocortisone therapy is given a tab of 2 x 40 mg po. Hydrocortisone is a glucocorticoid that can be used as a temporary therapy in patients with recurrent/persistent symptoms of severe hypoglycemia. Case studies show that oral hydrocortisone is effective in stabilizing blood glucose levels in insulinoma patients with recurrent/persistent hypoglycemia.

On day 5, hydrocortisone treatment tablets were replaced with methylprednisone injections at a dose of 2 x 31.25 mg intravenously. This aims to increase blood glucose so that the effect of hyperglycemia appears through the stimulation of gluconeogenesis in the liver, inhibiting glucose uptake by peripheral tissues and activating lipolysis and proteolysis as energy raw materials so that this is useful to reduce the symptoms of temporary hypoglycemia in these patients. Patients are also given PPI group therapy such as omeprazole caps 2 x 20 mg to protect the gastric mucosa and prevent ulcerative complications (Endocrine Society, 2023; Chair et al., 2023; Metz & Jensen, 2008).

The patient's mother suffered from a history of type 2 diabetes mellitus, but the patient did not have DM disease and was evidenced by no clinical symptoms and in the supporting examination in the form of gds ranged from 35 mg/dL, - 145 mg/dL without taking type 2 diabetes mellitus drugs.

This patient has experienced weight gain from 80 kg to 85 kg since the last 4 months, due to excessive food intake due to a response to hypoglycemia symptoms. According to a 2019 Japanese retrospective study, of 19 patients with a diagnosis of insuloma, 8 patients (42%) experienced weight gain before surgery (Shinden et al., 2019). According to the StatPearls guidebook, weight gain was found in most insulinoma patients (20-40%) (Zhuo et al., 2025).

Abdomen CT scan and without contrast and contrast abdominal MRI in this patient found no visible mass image in the pancreas. According to Durairaj et al., about 90% of insulinomas have a size of <2 cm and many of them are <1 cm, making them difficult to detect with conventional CT/MRI. The sensitivity of CT Scan reaches 63-94% and MRI 56-90%, but for lesions <1 cm the sensitivity can be below 60%. Meanwhile, according to Shiwei Luo et al., some insulinomas do not show a clear contrast enhancement (iso or hyposkuller) so there is no difference from normal pancreatic tissue (Arjunan et al., 2024; Luo et al., 2025).

Diagnosis enforcement also requires the determination of the location of the tumor using non-invasive imaging modalities such as CT scan, abdominal ultrasound, and MRI; if the non-invasive results do not show lesions, then invasive methods such as endoscopic ultrasonography (EUS) with high sensitivity (85-95%) can be used to detect small insulimoa, selective arterial calcium stimulation test (SACST) is the gold standard functional if non-diagnostic imaging, and GLP-1R PET/CT receptor imaging with sensitivity (93-98%) and high specificity >95% for patients with positive biochemical hypoglycemia, CT/MRI was negative and detected benign insulinoma, including lesions of <1 cm (Zhuo et al., 2025). In this patient, follow-up examination could not be carried out because Arifin Achmad Hospital did not have more complete facilities such as EUS/PET-CT/Biopsy, so the patient had to be referred to a hospital in the capital city of Jakarta.

The clinically and biochemically enforced insulinoma therapy algorithm is the first to ensure the stabilization of hypoglycemia with a high-carbohydrate diet, intravenous glucose infusion (D10% or inj. D40% when acute, diazoxide at a dose of 50-600 mg/day is divided into 2-3 doses which is the first line to suppress the secretion of endogenous insulin, a diuretic (hydrochlorothiazide) to prevent fluid retention, due to the main side effects of diazoxide. The second is the evaluation of resectibility by enucleation, segmental and laparoscopic pancreatectomy. The next for additional therapy in refractory or metastatic disease is the administration of Everolimus, Peptide Receptor Radionuclide Therapy (PRRT Lu-177), chemotherapy (streptozotocin + doxorubicin) and local ablation (EUS-RFA) (Falconi et al., 2023; National Comprehensive Cancer Network, 2025).

Conclusion

A 49-year-old female patient presenting with persistent hypoglycemia was clinically diagnosed with insulinoma, as evidenced by blood glucose levels below 55 mg/dL, insulin levels ≥ 55 μIU/mL, and C-peptide ≥ 0.6 ng/mL, indicating hypoglycemic hyperinsulinemia characteristic of insulinoma. Although non-invasive imaging methods such as contrast-enhanced CT and MRI failed to detect tumor lesions, diagnosis was further pursued using invasive techniques like endoscopic ultrasonography (EUS), selective arterial calcium stimulation test

(SACST), or GLP-1 receptor PET/CT imaging to localize the tumor. The patient showed clinical and laboratory improvement following treatment and was discharged on methylprednisolone and omeprazole. Future research should focus on evaluating and optimizing minimally invasive imaging modalities with higher sensitivity and specificity for tumor localization in insulinoma cases, especially in patients with negative findings on conventional imaging, to improve diagnostic accuracy and guide treatment.

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