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Recurrent Hypoglycemia Secondary to Pancreatic Insulinoma

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INTRODUCTION

Insulinomas are insulin-secreting pancreatic neuroendocrine tumors arising from pancreatic islet cells and are the most common cause of endogenous hyperinsulinemic hypoglycemia.[1] They produce hypoglycemia through autonomous insulin secretion that is independent of normal glucose-mediated regulation, resulting in increased peripheral glucose uptake and suppression of hepatic glucose production.[2] Although insulinomas are the most common functional pancreatic neuroendocrine tumors, they are rare, with an annual incidence of approximately one to four cases per million people.[3] Most are solitary lesions measuring less than 2 cm in diameter and often present with nonspecific symptoms, including visual disturbances, altered mental status, diaphoresis, and weakness, making diagnosis challenging.[1,4,5] Diagnosis is confirmed by demonstrating inappropriate insulin secretion during a supervised 72-hour fast, followed by imaging studies to localize the tumor.[6] Surgical resection remains the definitive treatment, with the operative approach determined by the tumor's size and anatomical location.[7,8] We report a case of recurrent hypoglycemia caused by an insulinoma arising in the pancreatic uncinate process that was successfully treated with pancreaticoduodenectomy.

CASE REPORT

A 61-year-old man with a history of paroxysmal atrial fibrillation and chronic lymphocytic leukemia (not receiving treatment) presented with recurrent severe hypoglycemia. He reported a one-year history of episodic hypoglycemia confirmed by home blood glucose monitoring. One week before presentation, he developed progressive nausea, fatigue, weakness, lightheadedness, and blurred vision, culminating in a fall that resulted in minor injuries. On admission, his serum glucose level was 33 mg/dL, requiring continuous intravenous dextrose infusion. Attempts to discontinue the infusion were unsuccessful, as his glucose level declined to 40 mg/dL after cessation, prompting further evaluation.

Laboratory testing showed a hemoglobin A1c of 5.2%, with normal cortisol (16.81 µg/dL) and thyroid-stimulating hormone (2.4 mU/L)

levels. Because of persistent hypoglycemia, a supervised 72-hour fast was initiated. The patient developed symptomatic hypoglycemia approximately two hours after discontinuation of intravenous dextrose. At the time of hypoglycemia, C-peptide (4.1 ng/mL), insulin (7.5 μU/mL), and proinsulin (23 pmol/L) levels were inappropriately elevated. Beta-hydroxybutyrate was suppressed at 0.1 mmol/L, consistent with endogenous hyperinsulinemia. Screening for exogenous hypoglycemic agents was negative.

Computed tomography (CT) of the abdomen and pelvis demonstrated a small enhancing lesion in the pancreatic head, raising concern for a pancreatic neuroendocrine tumor (Figure 1). Dedicated pancreatic imaging confirmed the lesion. The patient's hypoglycemia was medically managed with diazoxide while definitive surgical treatment was planned. He subsequently underwent exploratory laparotomy with pancreaticoduodenectomy (Whipple procedure), cholecystectomy, appendectomy, and regional lymph node sampling. Intraoperatively, a 1-cm lesion was identified in the uncinate process of the pancreas, and frozen section analysis confirmed a neuroendocrine tumor. Blood glucose levels normalized during the procedure without the need for additional dextrose administration, and sampled lymph nodes were negative for metastatic disease.

Gross examination revealed a well-circumscribed pancreatic mass measuring 0.8 × 0.6 × 0.4 cm that was confined to the pancreas. Histopathologic evaluation demonstrated a well-differentiated pancreatic neuroendocrine tumor, World Health Organization (WHO) Grade 1. No lymphovascular invasion, perineural invasion, or tumor necrosis was identified (Figures 2-4). Immunohistochemical staining was positive for synaptophysin, chromogranin, and INSM1, confirming the diagnosis. A Ki-67 proliferation index of <3% was consistent with low-grade disease (Figures 4 and 5).

At outpatient follow-up, the patient remained euglycemic without recurrent hypoglycemic episodes. His hemoglobin A1c increased to 6.1%, within the prediabetic range, warranting continued monitoring. Four months after surgery, positron emission tomography demonstrated no evidence of residual or metastatic disease.

DISCUSSION

Whipple's triad, (1) symptoms of hypoglycemia, (2) documented low plasma glucose at the time of symptoms, and (3) resolution of symptoms following glucose administration, was first described by Whipple and Frantz in 1935 and remains the cornerstone for diagnosing suspected insulinoma.[1] Our patient fulfilled all three criteria, presenting with recurrent hypoglycemic symptoms, including dizziness, blurred vision, and falls; documented episodes of severe hypoglycemia; and prompt symptom resolution following dextrose administration.

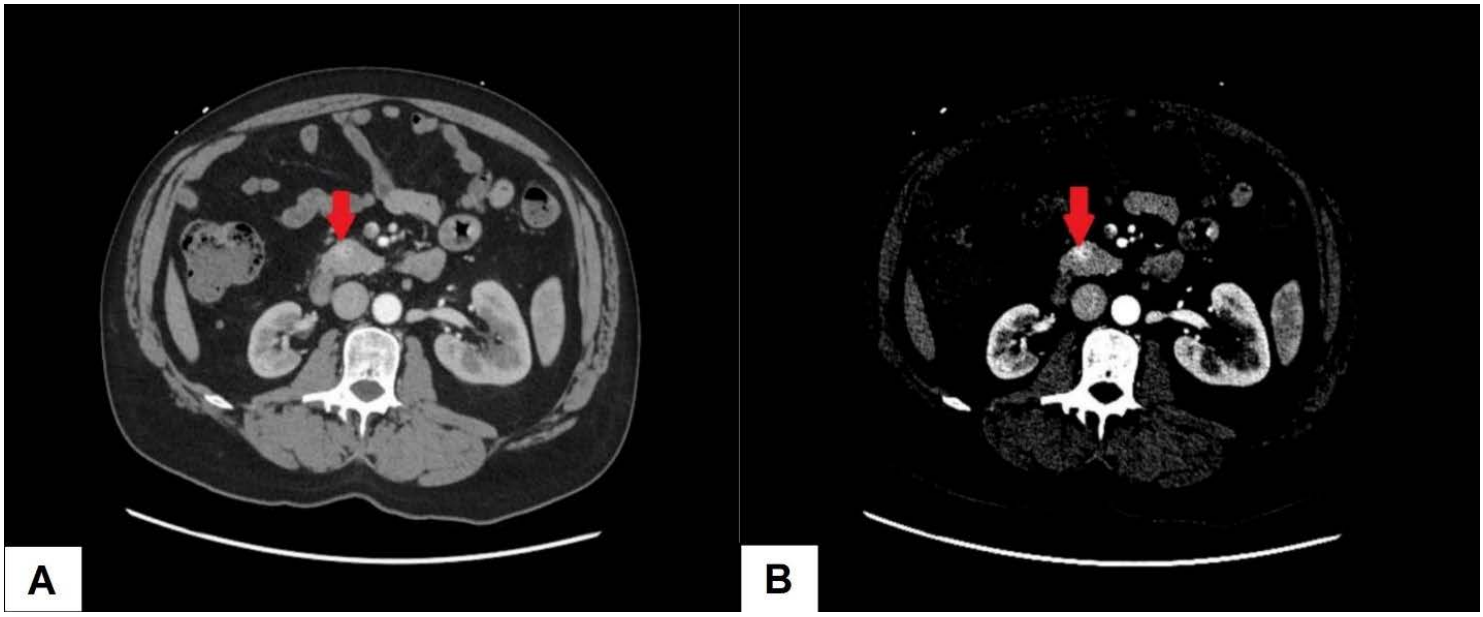

Figure 1. Contrast enhanced CT of the abdomen and pelvis demonstrating an enhancing lesion of the pancreatic head measuring approximately 1.4 x 1.3 cm, suspicious for a pancreatic neuroendocrine tumor. (A) Abdominal window. (B) Liver window.

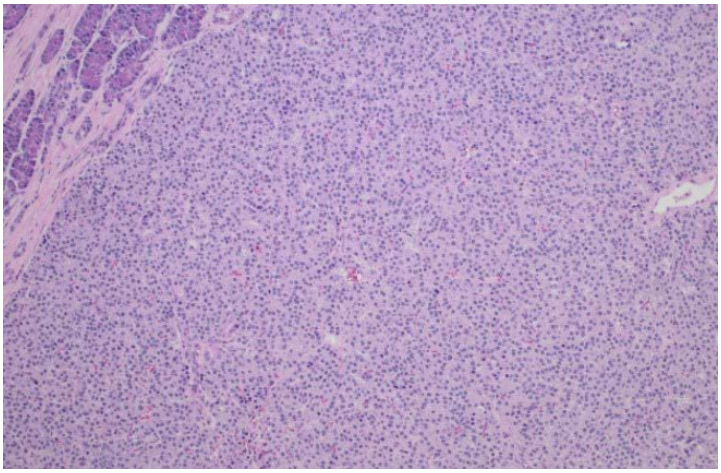

Figure 2. 4x histologic view showing a well-circumscribed tumor within the pancreatic parenchyma.

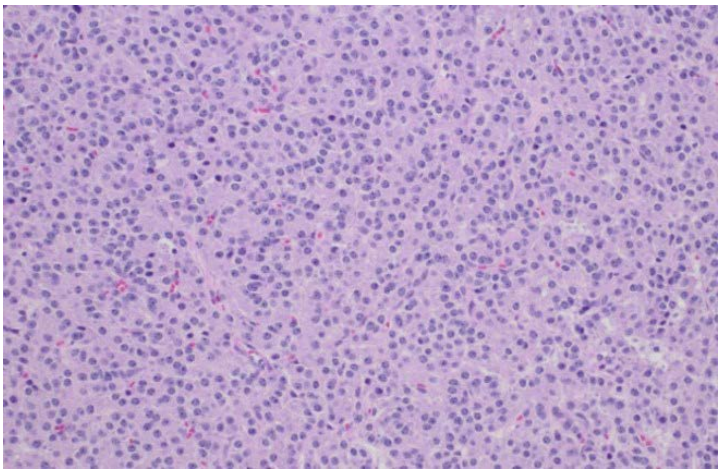

Figure 3. 20x histologic view showing nests and cords of uniform cells with round nuclei and speckled "salt and pepper" chromatin, characteristic of neuroendocrine tumors.

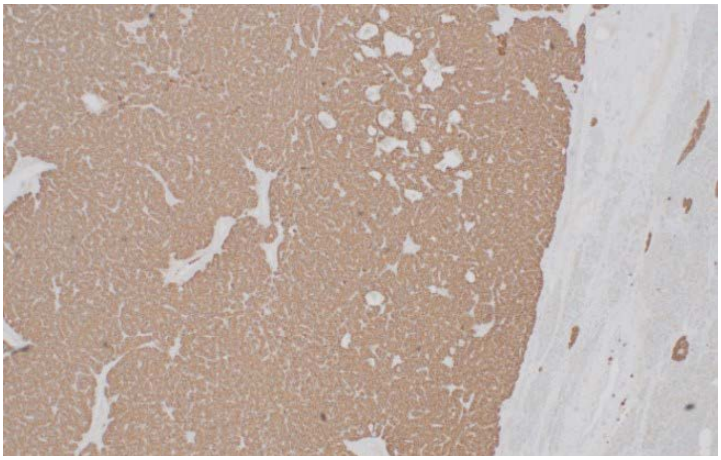

Figure 4. Immunohistochemical stain synaptophysin highlighting tumor cells, supporting neuroendocrine differentiation.

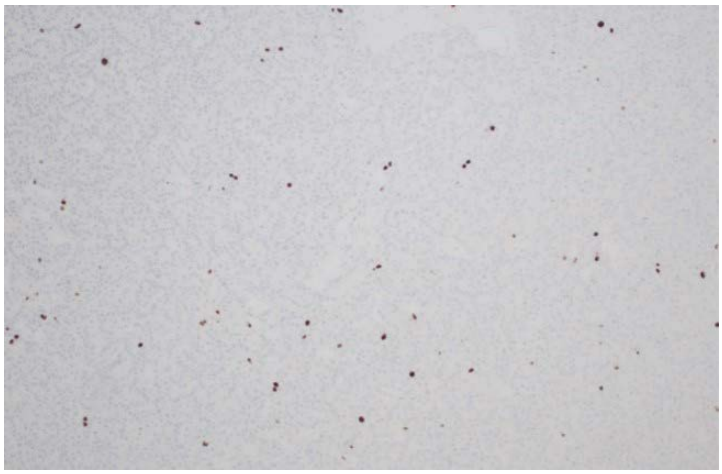

Figure 5. Immunohistochemical stain Ki-67 demonstrating a proliferation index of <3%. In combination with a mitotic rate of <2 mitoses per 2mm2, this pancreatic neuroendocrine tumor was classified as a WHO Grade 1.

Despite a year-long history of episodic hypoglycemia, the diagnosis was likely delayed because of the nonspecific nature of the patient's symptoms. Progressive, recurrent hypoglycemia requiring continuous dextrose infusion prompted a comprehensive endocrine evaluation. A supervised 72-hour fast was initiated but terminated early because of symptomatic hypoglycemia. During hypoglycemia, insulin, C-peptide, and proinsulin levels were inappropriately elevated, while screening for exogenous hypoglycemic agents was negative, supporting endogenous hyperinsulinemia. Subsequent imaging identified a pancreatic lesion, and the diagnosis of insulinoma was definitively confirmed by postoperative histopathology.

The differential diagnosis of hyperinsulinemic hypoglycemia includes insulinoma, factitious hypoglycemia, insulin autoimmune syndrome, and non-insulinoma pancreatogenous hypoglycemia syndrome.[7,9,10] In this case, the biochemical findings obtained during the supervised fast, together with negative screening for exogenous hypoglycemic agents and subsequent imaging and pathologic findings, strongly supported insulinoma as the underlying cause.

Most insulinomas are small, solitary, benign pancreatic neuroendocrine tumors that present with nonspecific neuroglycopenic and autonomic symptoms, frequently contributing to delayed diagnosis.[5,8,11] Clinical evaluation begins with confirmation of Whipple's triad, followed by biochemical testing to determine whether hypoglycemia

is insulin-mediated. A supervised fasting study demonstrated inappropriately elevated insulin, C-peptide, and proinsulin levels during hypoglycemia, together with suppressed beta-hydroxybutyrate and exclusion of exogenous hypoglycemic agents, strongly supports endogenous hyperinsulinism.[11] Imaging studies are then used to localize the lesion before surgery.[9] This diagnostic sequence closely mirrored our patient's clinical course. Malignant insulinomas have been associated with more rapid symptom onset and higher insulin, proinsulin, and C-peptide concentrations at the glucose nadir than benign tumors.[11,12]

The small size of most insulinomas, with the majority measuring less than 2 cm at diagnosis, can make localization challenging.[1,7] In this patient, contrast-enhanced computed tomography successfully identified an enhancing lesion within the pancreatic head that was subsequently confirmed intraoperatively. Although conventional imaging was sufficient in this case, equivocal lesions may require additional localization techniques, including endoscopic ultrasound or selective arterial calcium stimulation.[7,10] Previous study has reported localization rates of approximately 84% for CT and 79% for magnetic resonance imaging (MRI).[13] When combined, these imaging modalities achieve localization rates approaching 97%, suggesting that complementary imaging may improve preoperative localization when initial studies are inconclusive.[13]

Although most insulinomas occur sporadically, approximately 5% are associated with inherited endocrine syndromes, most commonly multiple endocrine neoplasia type 1 (MEN1).[3,14] MEN1 is an autosomal dominant disorder characterized by primary hyperparathyroidism, pancreatic neuroendocrine tumors, and pituitary adenomas.[8,14] It most commonly results from pathogenic variants in the *MEN1* gene, which encodes the tumor suppressor protein menin, a key regulator of cellular growth and genomic stability.[1] Compared with sporadic tumors, insulinomas associated with MEN1 are more likely to recur, metastasize, and be larger at diagnosis.[3,8,14] They also tend to present at a younger age, with approximately 25% occurring before 20 years of age.[14] Because pancreatic neuroendocrine tumors account for a substantial proportion of MEN1-related mortality, screening for pancreatic neuroendocrine tumors is recommended in both symptomatic and asymptomatic patients with MEN1.[14] Although MEN1 testing was not documented for our patient, evaluation for MEN1 should be considered in patients diagnosed with insulinoma, particularly those with early-onset disease, multifocal tumors, or a suggestive family history.[3,8,14]

Surgical resection remains the definitive treatment for localized insulinoma and is associated with excellent long-term outcomes.[1,7,15] Our patient underwent pancreaticoduodenectomy with complete tumor excision, resulting in intraoperative normalization of blood glucose levels and sustained postoperative resolution of hypoglycemia. Histopathologic examination demonstrated a well-differentiated pancreatic neuroendocrine tumor, WHO Grade 1, without lymphovascular invasion, perineural invasion, or tumor necrosis. These findings are consistent with the favorable prognosis observed in most localized insulinomas.[9] Studies have shown that the majority of insulinomas are localized at diagnosis and that surgical resection results in complete resolution of hypoglycemic symptoms in most patients.[8,16] Benign insulinomas typically are small, solitary lesions associated with low recurrence rates, whereas malignant tumors are more commonly characterized by larger size, metastatic disease, and poorer long-term outcomes.[9-12]

Although the tumor in this case was small, its location within the uncinate process placed it in close proximity to critical vascular and biliary structures. The operative approach was therefore determined based on anatomic considerations and intraoperative findings. While parenchyma-sparing procedures such as enucleation are preferred for appropriately located small insulinomas, pancreaticoduodenectomy may be necessary when local excision cannot be performed safely.[17]

Medical therapy remains an important option for patients who are poor surgical candidates, have unresectable disease, or require symptom control before surgery. Treatment options include frequent carbohydrate intake, diazoxide to suppress insulin secretion, and somatostatin analogs in selected patients.[18] Although our patient received diazoxide during hospitalization, persistent hypoglycemia necessitated continued intravenous dextrose infusion until definitive surgical resection.

A 60-year Mayo Clinic experience demonstrated that recurrence following complete resection of benign insulinoma is uncommon and that long-term survival is excellent.[6] Improved localization techniques have further contribut-

ed to favorable surgical outcomes. Consistent with these findings, our patient experienced complete resolution of hypoglycemia following surgery and remained euglycemic without the need for dextrose supplementation or antihypoglycemic therapy. At follow-up, the hemoglobin A1c had increased to the prediabetic range (6.1%), warranting continued metabolic surveillance.

This case underscores the importance of maintaining a high index of suspicion for insulinoma in patients with recurrent, unexplained hypoglycemia. Early recognition, appropriate biochemical evaluation, timely localization, and definitive surgical management are essential to prevent recurrent neuroglycopenic events and reduce the morbidity associated with delayed diagnosis.

CONCLUSIONS

This case highlights the importance of considering insulinoma in patients with recurrent, unexplained hypoglycemia accompanied by biochemical evidence of endogenous hyperinsulinism. Because symptoms often are intermittent and nonspecific, diagnosis may be delayed without a structured endocrine evaluation. Confirmation of Whipple's triad, appropriate biochemical testing, and timely tumor localization are essential for establishing the diagnosis and guiding management. Although surgical resection remains the definitive treatment for most localized insulinomas, this case also illustrates the importance of multidisciplinary collaboration in the evaluation and management of pancreatic neuroendocrine tumors. Prompt diagnosis and definitive treatment can result in complete resolution of hypoglycemia, reduce the risk of recurrent neuroglycopenic events, and provide excellent long-term outcomes.

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