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A RARE CASE OF RECURRENT HYPOGLYCEMIA DIAGNOSED AS INSULINOMA WITH HEPATIC METASTASIS

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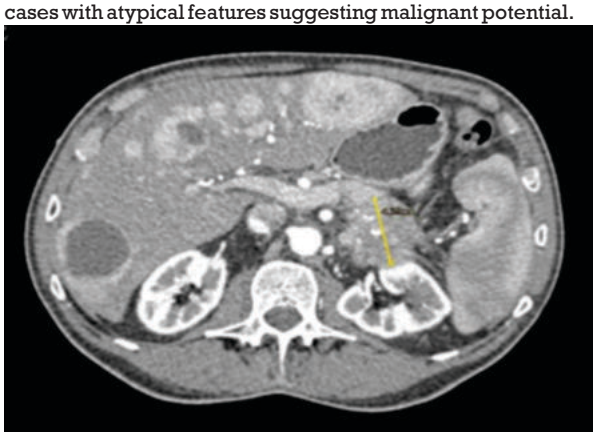
ABSTRACT

A 32-year-old male presented with recurrent episodes of hypoglycemia manifesting as profuse sweating and giddiness, which improved with carbohydrate intake. Initial evaluation revealed severe hypoglycemia (blood glucose 30 mg/dL) with elevated fasting insulin (33.6 micro IU/mL) and C-peptide (2.24 ng/mL) levels. Imaging studies, including CECT abdomen and DOTA- PET, revealed a 4.3×3 cm pancreatic tail mass with hepatic metastases showing somatostatin receptor expression. CT-guided liver biopsy confirmed a well-differentiated grade IIb insulinoma (MIB1 index 16%), positive for neuroendocrine markers. Initial management with continuous dextrose infusion and octreotide therapy provided limited glycemic control. The patient subsequently underwent transarterial embolization for liver metastases followed by oral capecitabine therapy. Despite initial resistance to treatment, the addition of diazoxide successfully stabilized blood glucose levels, allowing complete weaning from dextrose infusion. After several months of inpatient care, the patient was discharged with stable glycemic control and continued follow-up. This case illustrates the effectiveness of a multi-modal treatment approach in managing metastatic insulinoma and highlights the importance of systematic evaluation in cases of refractory hypoglycemia.

INTRODUCTION

Insulinomas are rare neuroendocrine tumors of the pancreas with an estimated incidence of 1-4 cases per million person-years [1]. These tumors are characterized by autonomous insulin secretion leading to recurrent hypoglycemic episodes, which can significantly impact a patient's quality of life [2]. While most insulinomas are benign and solitary, approximately 5-10% are malignant with the potential for metastatic spread, most commonly to the liver [3]. The diagnosis of insulinoma presents a clinical challenge due to its nonspecific symptoms and the need for specialized biochemical and imaging studies [4]. The classic Whipple's triad - symptoms of hypoglycemia, low blood glucose levels, and relief of symptoms with glucose administration - remains a cornerstone in the initial clinical suspicion[5]. However, when complicated by metastatic disease, the clinical presentation and management become more complex, requiring a multidisciplinary approach [6]. We present a rare case of metastatic insulinoma with hepatic involvement, highlighting the diagnostic challenges and management considerations in this uncommon presentation. This case underscores the importance of considering insulinoma in the differential diagnosis of recurrent hypoglycemia, even in cases with atypical features suggesting malignant potential.



Abdominal computerized tomography scan:solid 4.3*3cm nodule in the tail of the pancreas(arrow)

CASE STUDY

A 32-year-old male presented to the emergency department with complaints of profuse sweating and giddiness. The patient reported experiencing multiple similar episodes over the previous two months, with symptoms improving upon consumption of candy or fruit juice. On presentation, the patient was drowsy with a Glasgow Coma Scale score ≥12 and had normal vital signs. Initial laboratory investigation revealed severe hypoglycemia with a blood glucose level of 30 mg/dL. The patient denied any use of hypoglycemic agents. Given the severity of presentation, the patient was admitted for management of severe hypoglycemia. Further diagnostic workup revealed elevated fasting insulin levels of 33.6 micro IU/mL, C-peptide of 2.24 ng/mL, and markedly elevated chromogranin A levels of 1035 ng/mL. Contrast-enhanced CT of the abdomen demonstrated a 4.3 x 3 cm pancreatic mass in the tail region along with multiple hypoenhancing lesions in the liver. DOTA-PET scan confirmed somatostatin receptor expression in both the distal pancreas (primary site) and liver, indicating the secretory function of the tumor. CT-guided liver biopsy confirmed the diagnosis of a well-differentiated grade IIb insulinoma with an MIB1 labeling index of 16%. Immunohistochemistry was positive for CK19, CDX2, synaptophysin, and chromogranin A, supporting the neuroendocrine origin of the tumor.

Initial management included continuous D5% infusion at 80 mL/hr with supplemental D25% 100 mL IV as needed for blood glucose levels below 70 mg/dL. Octreotide was initiated at 50 mg TDS and gradually uptitrated to 200 mg TDS. Despite these interventions, the patient continued to experience recurrent hypoglycemic episodes, necessitating frequent carbohydrate intake approximately 7-8 times daily. This poor response to initial management prompted further therapeutic interventions. Given the refractory nature of hypoglycemia and the presence of hepatic metastases, a multidisciplinary team discussion was conducted. The patient underwent transarterial embolization for liver metastases and was started on oral capecitabine 1000mg twice daily for 14 days. Following this, the dextrose infusion requirement was gradually reduced to 20 mL/hr, though blood glucose levels remained uncontrolled. Subsequently, the patient was started

on diazoxide 50mg TDS, which helped stabilize blood glucose levels by inhibiting insulin secretion. Eventually, the patient was successfully weaned off dextrose infusion, with normalization of both fasting and postprandial blood glucose levels. After several months of inpatient care, the patient was dischargedwith arrangements for continued medical monitoring and follow-up.

DISCUSSION:

The present case highlights several important aspects of metastatic insulinoma, including its clinical presentation, diagnostic approach, and management challenges. Our patient presented with classical Whipple's triad, which is observed in approximately 75% of insulinoma cases [7]. The significantly elevated fasting insulin level of 33.6 micro IU/mL and C-peptide of 2.24 ng/mL in our case aligns with the diagnostic criteria established by the Endocrine Society guidelines, which suggest that elevated insulin levels (>3 U/mL) with concurrent hypoglycemia are diagnostic of inappropriate insulin secretion [5]. The malignant potential in our case was evidenced by the presence of hepatic metastases, which occurs in approximately 5-10% of insulinomas [8]. The size of the primary tumor (4.3 x 3 cm) in our patient was notably larger than the typical insulinoma, which usually measures less than 2 cm. This finding supports previous studies suggesting that tumor size >2 cm is associated with increased risk of malignancy and metastatic potential [9]. The elevated chromogranin A level of 1035 ng/mL in our patient served as both a diagnostic marker and prognostic indicator, consistent with findings by Gut et al., who demonstrated that chromogranin A levels correlate with tumor burden and metastatic potential in neuroendocrine tumors [10]. The management approach in our case required a multi-modal strategy due to the refractory nature of hypoglycemia. While octreotide therapy is considered first-line medical management for metastatic insulinomas, with reported response rates of 35-50% [11], our patient showed only partial response despite dose escalation to 200 mg TDS. This resistance to somatostatin analog therapy has been documented in other cases, particularly in tumors with high proliferative indices [12]. The implementation of transarterial embolization (TAE) for hepatic metastases in our case follows emerging evidence supporting its efficacy in managing neuroendocrine liver metastases. A systematic review by Kaltsas et al. reported symptom improvement in 73- 100% of cases following hepatic arterial embolization [13]. The addition of capecitabine in our treatment protocol aligns with current recommendations for systemic therapy in progressive metastatic disease [14].

The use of diazoxide as a glucose-stabilizing agent proved crucial in our case. This aligns with previous reports showing efficacy rates of 50-60% in controlling hypoglycemia in insulinoma patients [15]. Our case also emphasizes the value of a multidisciplinary approach in managing complex neuroendocrine tumors, as documented by Pavel et al. [6].

CONCLUSIONS:

This case highlights the diagnostic and therapeutic challenges in managing metastatic insulinoma with refractory hypoglycemia. The successful outcome demonstrates the importance of a multi-modal treatment approach, combining medical management with interventional procedures. The sequential use of octreotide, transarterial embolization, systemic chemotherapy, and diazoxide proved effective in achieving glycemic control. This case emphasizes the critical role of a multidisciplinary team approach in managing complex neuroendocrine tumors and underscores the importance of considering insulinoma in the differential diagnosis of recurrent hypoglycemia, particularly when presenting with atypical features or signs of malignancy.

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