Insulinoma is a rare neuroendocrine tumor (NET) originating from hypersecreting beta-(β)-cells of islets of Langerhans in the pancreas, causing hyperinsulinism, with an overall incidence of 1 in 1 million per year. They usually present with symptoms of hypoglycemia but rarely with atypical features like refractory recurrent secondary generalized seizures and behavioral disturbances with increased irritability, initially mistreated as alcohol withdrawal. Detailed history, particularly the relationship of the symptoms with food intake, made us think of other causes of seizures. Fasting biochemical investigations and localizing studies helped clinch the diagnosis. The tumor was localized with the help of endoscopic ultrasonography and whole-body Ga68-DOTANOC PET-CT. The patient was treated conservatively with diazoxide and is doing well on follow-up. The present case report emphasizes the importance of detailed clinical history, more so in atypically presenting cases of refractory seizures. Insulinoma can be medically managed despite surgery being the gold standard curative treatment.

Case History

A 72-year-old male patient, farmer by occupation, presented to the out-patient department with recurrent episodes of secondarily generalized seizures for 20 months. His wife reported having observed seizures more frequently in the morning especially after consuming alcohol the previous day. On further probing, she also admitted that the patient was irritable and became short-tempered recently. The patient was treated, by local physicians, with benzodiazepines (lorazepam, chlordiazepoxide) and antiepileptic drugs (carbamazepine, sodium valproate). He was treated with anti-tubercular therapy (ATT) for his ileocecal TB 27 years ago. He did not have any significant medical history nor any comorbidities including diabetes mellitus. Apart from regular ethanol consumption with frequent binging, he denied any other substance abuse. Family history was negative for any seizure disorder. On examination, the patient’s vitals were stable and his higher mental functions were normal with no focal neurological deficits.

Routine investigations turned to be normal at admission. But the patient had a blood glucose of 62 mg/dL the next morning. His serum cortisol and thyroid profile were within a normal range. Patient was advised to fast under strict observation. His fasting serum insulin and c-peptide levels were increased, when blood glucose was 42 mg/dL [Table 1].

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Triple phase CECT of the abdomen showed thickened cecal wall and no masses in the pancreas [Figure 1]. Done with a strong suspicion of insulinoma, endoscopic ultrasound (EUS) of the pancreas revealed a 6 × 9 mm lesion in the uncinate process of the pancreas [Figure 2]. Whole-body Ga68-DOTANOC PET CT confirmed the mass to be metabolically active NET [Figure 3]. The patient being frail denied surgery for the removal of the mass. A diagnosis of benign solitary sporadic insulinoma was made clinically after screening for Multiple Endocrine Neoplasia-type 1 (MEN-1) was negative. He was started on medical therapy with Diazoxide 100 mg TDS titrated to 200 mg TDS after 1 month of follow-up, was advised to stop ethanol consumption, and avoid fasting. The patient tolerated the drug and is doing well without symptomatic hypoglycemia episodes for the past 19 months.

**Discussion**

Insulinomas are the most common islet cell tumors (ICTs). They are usually solitary, benign, and sporadic, although 5–10% occur in patients with MEN-1; 10% are malignant featured by metastasis.[5] They are more common in the 5th and 6th decade of life, with slight female preponderance. Virtually all insulinomas are ICTs; however, there is one case report of insulin-secreting small cell carcinoma of the cervix.[6]

The defining feature of this tumor is the autonomous production of insulin resulting in hypoglycemia. They can present typically with neuroglycopenic symptoms like confusion, dizziness, loss of consciousness, visual changes, and/or sympathoadrenal symptoms like palpitations, sweating, tremulousness; can be associated with increased appetite and weight gain.[3] The hypoglycemia in patients with insulinoma is primarily because of reduced hepatic glucose output rather than increased glucose utilization.[7] In a retrospective study of 59 patients by Dizon et al. with histologically confirmed islet cell adenomas, the interval between onset of symptoms and diagnosis ranged from 1 month to 30 years, with a median of 24 months and the most common symptoms at presentation were confusion (83%) followed by diaphoresis (69%).[3]

In our case, patient had an atypical presentation[8] with recurrent secondary generalized seizures and behavioral disturbances with increased irritability. Alcohol abuse itself can cause hypoglycemia by starvation, inhibition of gluconeogenesis and also withdrawal seizures, typically 6–48 h after last drink. History of chronic alcohol abuse, in this case, masqueraded the patient’s primary cause of hypoglycemia leading to delayed diagnosis. Careful history

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Table 1: Biochemical investigation results during the supervised fast

| Test                        | Value                  |
|-----------------------------|------------------------|
| Blood glucose (by Hexokinase) | 42 mg/dL              |
| Serum insulin (by CIMIA)    | 3.60 µIU/mL (>3 µIU/mL)* |
| Serum C-peptide (by CLIA)   | 2.02 ng/mL (>0.6 ng/mL)* |

*Cut-off levels for insulinoma during fasting when blood glucose is <55 mg/dL, CMIA: Immunochemistry assay, ICMA: Immune-chemistry assay

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Figure 1: Axial CECT abdomen image taken in arterial phase showing no visible masses in the uncinate process of the pancreas (red arrow)

Figure 2: Endoscopic ultrasonography (EUS) showing pancreatic duct (red arrow) and a small 6 mm × 9 mm hypo to iso echoic lesion noted in uncinate region of pancreas (measured by D1 and D2)

Figure 3: Whole body Ga68-DOTANOC PET-CT showing sub-centimetric sized mildly prominent tracer uptake (max SUVbw of 3.74 g/ml) in the uncinate region of pancreas (red arrow) on fusion images in axial section
taking regarding the relation of food intake to seizures made us think of other causes. The presence of Whipple’s triad should prompt us to evaluate for hyperinsulinemic hypoglycemia, with prolonged supervised fasting up to 72 h. C-peptide levels, insulin levels, pro-insulin, β-Hydroxybutyrate, glucose levels in the blood; the response of blood glucose to IV injection of 1 mg glucagon; screening for anti-insulin antibodies and oral hypoglycemic agents like sulfonylureas in known diabetics or suspicion of factitious hypoglycemia should be done. An elevated or normal fasting plasma insulin level with normal or elevated C-peptide in the presence of hypoglycemia points to a diagnosis of insulinoma or NIPHS.

Multidetector CT can detect 94.4% of insulinomas, hence is currently accepted as the first-line investigation for the visualization of insulinomas. On CT they are hyper-vascular and enhance more than normal pancreatic parenchyma during the arterial and capillary phases of contrast bolus. Calcification, when it occurs, tends to be discrete and nodular, and is more common in malignant than benign tumors. 90% are solitary, 90% are <2 cm in diameter, and the tumors are distributed equally within the head, body, and tail of the pancreas. Among invasive localization modality, EUS is currently the test of choice in most Western centers, with reported detection rates of 86.6–92.3%. On EUS, they are quite characteristic, with most tumors homogeneously hypoechoic (rarely isoechoic), rounded in shape, and with distinct margins. Tissue sampling by EUS-guided fine needle aspiration biopsy (FNA) establishes a definitive diagnosis pre-operatively but required only in inconclusive cases, unlike our case. PET-CT imaging with Ga68-DOTANOC/DOTATATE, molecules having a high affinity to somatostatin receptors, can localize most of the tumors missed on anatomic imaging and to detect metastasis. Various other tracers like 18F-DOPA and Ga68 DOTA-exendin-4 can also be used.

In our case, we favored the diagnosis of insulinoma rather than non-insulinoma pancreatic endocrine hypoglycemic syndrome (NIPHS) based on the timing of symptoms (typically fasting for insulinoma and postprandial for NIPHS) and, ultimately, the results of localization studies (discrete solitary mass in insulinoma and diffuse in NIPHS). However, there is only one reported case with concurrent insulinoma and nesidioblastosis.

Surgical resection of the tumor is the gold standard curative treatment as most cases are benign. But when contraindicated as in metastatic disease, unfit patients and unwilling patients, and also for preoperative management of hypoglycemics, medical management is preferred. In the older frail patients, medical treatment with diazoxide is advised as the first-line of therapy. Freedom from episodes of hypoglycemias with diazoxide therapy is reported to be 59% in a study conducted by Gill et al. Common side effects were fluid retention (30%), hirsutism (11%), hypotension (2%), rash (2%). These side effects were well tolerated and the benefits of therapy were felt to outweigh disadvantages.

Insulinomas can also present with unusual symptoms of hypoglycemia causing misdiagnosis and unwarranted treatment, some risking adverse effects. Hence, the index of suspicion should be high if presented with atypical symptoms, particularly related to food intake; and a detailed clinical history is helpful. Most cases can be diagnosed by classical Whipple’s triad, positive biochemical tests on fasting, negative toxicology, typical pancreatic lesions on anatomical localization. And histological diagnosis by EUS-guided FNAC is required only in inconclusive or uncertain diagnosis. When gold standard surgical excision is contraindicated or awaited, medical therapy is effective. Early diagnosis and treatment can prevent fatal complications and irreversible brain damage because of neuroglycopenia.

Declaration of patient consent
The authors certify that appropriate patient consent was obtained.

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Conflicts of interest
There are no conflicts of interest.

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