A case report of insulinoma presenting with seizures and localized on endoscopic ultrasound

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Abstract

Insulinomas are rare functioning neuroendocrine tumors. Up to 10% of insulinomas are associated with multiple endocrine neoplasia 1 . Several non-invasive and invasive techniques are used to localize the lesion. We present a case of insulinoma presenting with seizures episode , with negative non-invasive imaging results ,diagnosed with endoscopic ultrasound.

Title: A case report of insulinoma presenting with seizures and localized on endoscopic ultrasound

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Abstract:

Introduction:

Insulinomas are rare functioning neuroendocrine (NEN) tumors. Up to 10% of insulinomas are associated with multiple endocrine neoplasia 1 (MEN1). Most of the tumors present with symptomatic hypoglycemia. Several non-invasive and invasive techniques are used to localize the lesion. We present a case of insulinoma presenting with seizure episodes with negative results on non-invasive imaging diagnosed and localized with endoscopic ultrasound.

Case presentation:

A 36 years old South Asian gentleman was brought by ambulance to the emergency department with an episode of generalized tonic-clonic seizures. At the time of the attack, the patient's blood glucose checked via point of care testing was 1.6mmol. He was given IV dextrose., Physical examination after the patient regained consciousness revealed a temperature of 36.8 °C, respiratory rate 20/minute, blood pressure 135/80, heart rate 76/minute and oxygen saturation of 99% in room air. Cardiac, respiratory, abdominal and neurological examination was normal. Hypoglycemia workup revealed a normal cortisol level, elevated insulin and c-peptide level consistent with hyperinsulinemia. An MRCP,NM 18F-DOPA whole-body PET CT and Ga-68 DOTATATE scan were normal and did not reveal any pancreatic lesion consistent with insulinoma. Due to high suspicion of insulinoma and negative non-invasive imaging, an endoscopic ultrasound (EUS) was performed, which showed a hypoechoic homogenous mass lesion sized 13x9 mm in the proximal body/neck of the pancreas. A fine needle biopsy (FNA) via EUS was performed. Histopathology showed a well-differentiated neuroendocrine tumor, consistent with Grade 1 insulinoma (T1N0M0). The patient underwent a distal pancreatectomy and splenectomy.

Conclusion:

In cases of high clinical and biochemical suspicion of insulinoma but negative non-invasive imaging, invasive modalities should be used to localize the culprit lesion.

Introduction:

Insulinomas are rare functioning neuroendocrine (NEN) tumors with an annual incidence of 1-4 cases per million. Up to 10% of insulinomas are associated with multiple endocrine neoplasia 1 (MEN1). Most of the tumors present with symptomatic hypoglycemia and the diagnosis is established by demonstrating endogenous hyperinsulinemia in the presence of hypoglycemia(1). Several non-invasive techniques are used to localize the lesion and include an ultrasound (US) abdomen, CT scan, MRI, and molecular imaging techniques like NM 18F-DOPA whole-body PET CT and Ga-68 DOTATATE scan(2-4). Due to the low sensitivity of the non-invasive methods, the localization of the tumor presents a diagnostic challenge, and invasive techniques like endoscopic ultrasound (EUS) and angiography and arterial stimulation venous sampling (ASVS) should be used if the suspicion is high(5, 6). We present a case of insulinoma presenting with seizure episodes. Laboratory testing revealed evidence of hyperglycemia, but all the non-invasive testing, including molecular imaging, was negative, and the diagnosis was established after localizing and fine-needle aspiration (FNA) of the tumor with EUS

Case Presentation:

A 36 years old South Asian gentleman was brought by the ambulance to the emergency department with an episode of a generalized tonic-clonic seizure. As per the witness, the patient was sitting when he suddenly collapsed and had jerky movements of his arms and legs. The episode lasted for about 5 minutes. There was no bowel or bladder incontinence. After the episode, the patient remained confused for 15-20 minutes. At the time of the seizure, the patient's blood glucose checked via point of care testing was 1.6mmol. He was given IV dextrose after the patient regained consciousness, he reported feeling sweaty and palpitations before the seizure episode. He denied any headache, neck pain, fever, dizziness, weakness, cough, rhinorrhea, sore throat, dysuria, nausea, vomiting or diarrhea.

The patient reported an off-and-on feeling of light-headedness in the last 2-3 months that improved after drinking juice. He did not have any chronic illnesses or previous surgeries. He denied taking any medications, including multivitamins or herbal remedies. The patient was a non-smoker and did not drink alcohol. There was no family history of malignancies. After the patient regained consciousness, physical examination revealed a temperature of 36.8 °C, respiratory rate of 20/minute, blood pressure of 135/80, heart rate of 76/minute, and oxygen saturation of 99% in room air. Cardiac, respiratory, abdominal and neurological examination was normal.

A basic laboratory workup revealed a normal complete blood count and metabolic and coagulation profile. Serum ethanol level was normal (table1). An MRI showed multiple calcified lesions in the brain concerning

neuro-cysticercosis, which did not require any treatment. During the hospital stay, the patient had multiple episodes of hypoglycemia.

Hypoglycemia workup revealed a normal cortisol level, elevated insulin and c-peptide level consistent with hyperinsulinemia. (table 2). An MRCP**,** NM 18F-DOPA whole-body PET CT and Ga-68 DOTATATE scan were normal and did not reveal any pancreatic lesion consistent with insulinoma. Due to high suspicion of insulinoma and negative non-invasive imaging, an EUS was performed, showing hypoechoic homogenous mass lesion sized 13x9 mm in the proximal body/neck of the pancreas (Figure 1). A FNA via EUS was performed. Histopathology showed a well-differentiated neuroendocrine tumor, consistent with Grade 1 insulinoma (T1N0M0). Patient underwent distal pancreatectomy and splenectomy. Upon follow up 2 months after the surgery, the patient reports no further episodes of hypoglycemia and is doing all his activities of daily living without any difficulty.

Discussion:

Insulinomas are well differentiated NEN that most commonly present with hypoglycemia. Other presenting features include seizures, altered sensorium, unexplained weight gain or abdominal pain. The median duration between symptoms onset and diagnosis range may range between 18 to 35 months(7). Although the majority of patients have fasting hypoglycemia, upto 21% patients report both fasting and post prandial hypoglycemia and 6% patients report exclusively post-prandial hypoglycemia(8). Nevertheless, the first step in evaluating hypoglycemia is to confirm the diagnosis by establishing Whipple's triad, which includes symptoms of hypoglycemia, plasma glucose concentration less than 55 mg/dl, and resolution of symptoms after correction of hypoglycemia(9). If the etiology of hypoglycemia is not evident based on initial history and physical examination, the further diagnostic workup includes measurement of plasma glucose, plasma insulin level, pro-insulin, C-peptide, beta-hydroxybutyrate (BHB) and screening for sulfonylureas during an episode of spontaneous hypoglycemia to assess for insulin-mediated versus non-insulin mediated hypoglycemia. In the absence of a spontaneous episode of hypoglycemia, a supervised 72-hour fast can be carried out to recreate a spontaneous hypoglycemia episode during which the above-mentioned laboratory evaluation can be performed. The hypoglycemia episode is then corrected with the administration of 1 mcg glucagon injection, and the response of glucose to glucagon injection is measured by checking serum plasma glucose level. These laboratory investigations will differentiate insulin (exogenous or endogenous) mediated hypoglycemia from hypoglycemia caused by other mechanisms (e.g., noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)). Anti-insulin antibodies can be tested to evaluate for autoimmune insulin hypoglycemia. A plasma glucose level of less than 55 mg/dl, insulin level more than 3 uU/ml, C-peptide more than 0.2 nmol/L, pro-insulin more than 5 pmol/L, beta-hydroxybutyrate less than 2.7 mmol/L with an increase in plasma glucose by more than 25 mg/dl, negative urine screen for sulfonylureas, serum insulin antibodies and negative history of previous bariatric surgery points towards insulinoma as the most probable etiology of endogenous hyperinsulinemic hypoglycemia (EHH)(10). A proposed approach to adult hypoglycemia evaluation based on endocrine society guidelines has been shown in algorithm 1(10). Hypoglycemia evaluation in our patient indicated insulinoma as the cause of hypoglycemia.

A number of non-invasive imaging modalities can be used to localize an insulinoma after the biochemical workup. These US abdomen, CT scan and MRI of the abdomen. The sensitivity of the US abdomen in localization of an insulinoma is reported to be 9-64%, CT scan 33-64% and MRI 40-90%(11). Up to 35% of patients with evidence of EHH have negative US, CT and MRI during the evaluation of insulinoma(2). Neuroendocrine tumors are rich in somatostatin receptors (SSR), especially SSR subtype 2. Hence, somatostatin receptor scintigraphy using octreotide is a vital imaging modality in localizing gastric neuroendocrine tumors. SSR, however, has low expression in insulinomas compared to other gastric neuroendocrine tumors and hence, octreotide scans have a high false-negative rate in cases of insulinoma(2). 68Ga-DOTATATE positron emission tomography/computed tomography (68Ga-DOTATATE PET) has shown a sensitivity of 95.1 % in the detection of gastric neuroendocrine tumors(3). 18F-DOPA PET is another imaging modality with a higher sensitivity rate of 90% in localizing the lesions in case of insulin-mediated hypoglycemia(4).

EUS and ASVS are invasive techniques to localize insulinoma when the non-invasive techniques fail, and

the suspicion remains high. EUS has a sensitivity of up to 89%, whereas the sensitivity of ASVS has been reported to be up to 93% (5, 6). Patel et al. reported 2 cases of insulinomas with negative imaging (including negative octreotide scan in one case). Both patients were diagnosed with FNA via EUS(12). Siddharth et al. also reported a case of insulinoma diagnosed with EUS who initially had a negative CT abdomen, MRI abdomen and octreotide scan(13). Our patient also had a negative US abdomen, CT abdomen, and MRI abdomen/MRCP. Given the high suspicion of a neuroendocrine tumor as the etiology of hypoglycemia, 18F-DOPA PET/CT and 68Ga-DOTATATE PET/CT were performed, which, despite being highly sensitive modalities, were negative making it extremely challenging to localize the tumor. Hence, the diagnosis was established with EUS followed by FNA of the lesion.

Conclusion:

Due to the variable sensitivity of non-invasive imaging modalities, the localization of insulinoma frequently presents a diagnostic challenge. In cases of high clinical and biochemical suspicion of insulinoma but negative non-invasive imaging, invasive modalities should be used to localize the culprit lesion.

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Statement of Ethics:

The case was approved by the medical research centre of Hamad Medical Corporation (HMC) with MRC-04-22-284

Conflict of Interest Statement

All authors have no conflict of interest.

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Data availability statement

N/A

Consent

Informed written consent was obtained from the patient for publication of this case report.

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Table 1

Variables	Results	Reference Range Adults
Blood :	Blood :	Blood :
Wbc (per µl)	8500	4000 - 11000
Hgb (g/dl)	14.8	13 - 17
Hematocrit (%)	44.9	40-50
Absolute Neutrophils Count (per µl)	5800	2000 - 7000
Lymphocyte Count (per µl)	2200	1000 - 3000
Platelets Count (per µl)	186000	150000 - 400000
PT (sec)	10.1	9.7 - 11.8
APTT (sec)	27.4	24.6 - 31.2
INR	0.9	N/A
Urea (mmol/L)	5.2	2.5 - 7.9
Creatinine (µmol/L)	61	62 - 106
Na (mmol/L)	142	135 - 145
K (mmol/L)	3.4	3.5 - 5.5
Cl (mmol/L)	105	95 - 105
HCO 3 (mmol/L)	26	22 - 28
Adjusted Calcium (mmol/L)	2.47	2.20 - 2.60

Table 1		
Mg (mmol/L)	0.94	0.75 - 1.0
Amylase (U/L)	20	25 - 125
Lipase (U/L)	73	13 - 60
Albumin (g/L)	41	35 - 55
Total Protien (g/L)	77	60 - 78
ALT (U/L)	16	8 - 20
AST (U/L)	17	8 - 20
Alk phosphatase (U/L)	127	40 - 129
Billirubin T (μmol/L)	7	2 - 17
Ethanol (mmol/L)	negative	<2.2
CRP (mg/L)	2.1	0 -5

Table 2 , Endocrinology results:

Morning Cortisol (nmol/L)	281	138 - 689
POC Glucose (mmol/L)	2.4	3.5 - 5.5
Insulin (mcunit/ml)	62.4	2.36 - 24.9
C-peptide (ng/ml)	8.13	1.1 - 4.4

Algorithm 1. Evaluation of hypoglycemia

BG: blood glucose, BHB: betahydroxybutyrate, NIPHS: non-insulinoma pancreatogenous hypoglycemia syndrome, PGBH: post gastric bypass hypoglycemia, IGF: insulin-like growth factor