CASE REPORT

Insulinoma; a diagnostic challenge: a case report

Wania Rafaey, Asim Munir Alvi, Sidra Aslam, Ahmed Imran Siddiqui, Waqas Shafiq

Abstract

Insulinoma is a pancreatic neuroendocrine tumour that primarily leads to episodes of hypoglycaemia due to inappropriate and excessive secretion of insulin. It classically presents with neuroglycopenic and autonomic sympathetic symptoms, which resolve promptly with glucose administration. Elevated level of insulin and C-peptide in the presence of low plasma glucose level and absence of plasma sulfonylurea are diagnostic features. Localisation of the tumour is essential before surgery. However, Insulinoma is difficult to diagnose due to its ambiguous location and insidious course. This is the case of a young male who had 6 months history of adrenergic and neuroglycopenic symptoms, including one episode of seizure. His symptoms resolved with the consumption of high glycaemic indexed food. Biochemical tests were suggestive of insulinoma, but non-invasive imaging techniques including computer tomography (CT) and magnetic resonance imaging (MRI) could not localise the tumour. In this case, pancreatic insulinoma was localised by endoscopic pancreatic ultrasound (EUS). He underwent successful resection of the tumour and his symptoms resolved completely post-surgery.

Keywords: Insulinoma, insulin levels, endoscopic ultrasound.

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Introduction

An insulinoma is a rare endocrine tumour of the pancreas. It causes hypoglycaemia through its autonomous secretion of insulin. It is a very rare tumour, with an annual incidence of 1- 32 per million population.[1] Insulinoma is usually a benign tumour, sporadic in origin and presents with a solitary small mass (< 2cm diameter).[2] Insulinomas are found with equal frequency in the head, body and tail of the pancreas. Symptoms of hypoglycaemia include both adrenergic symptoms (pallor, sweating, tremors and tachycardia) and neuroglycopenic symptoms (irritability, confusion, aggression, seizures and coma). Whipple's triad should be confirmed as part of the diagnostic workup, but be aware that over time, hypoglycaemia unawareness may develop and potentially confound the clinical picture. Early localisation of the tumour is essential to prevent fatal hypoglycaemia.

The gold standard test for biochemical diagnosis is a 72-hours fasting to check plasma glucose, insulin, C-peptide and proinsulin. Imaging modalities used to localize the tumour include computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), intra-arterial calcium stimulation with hepatic venous sampling or angiography, and arterial stimulation venous sampling (ARVS). Diagnosis of this rare disease requires high index of suspicion based on clinical and laboratory findings and imaging to localize the lesion. However, sometimes biochemically proven cannot be localized with CT scan or MRI abdomen. In that case, Endoscopic ultrasound (EUS) should be considered as the next imaging modality to localize the tumour.

Case presentation

A 24 years old male medical student, presented to the Endocrinology clinic of Shaukat Khanum Memorial Cancer Hospital and Research Centre in January 2019 with 6 months history of sweating, tremors, palpitations, dizziness, recurrent episodes of documented hypoglycaemia, one episode of seizures (both adrenergic and neuroglycopenic symptoms), and improvement of symptoms after taking high glycaemic indexed foods. Hypoglycaemic episodes mostly occurred during fasting and after exercise. His appetite had increased and he had gained almost 20kg weight in 6 months. There was no history of recurrent abdominal pain, nausea, vomiting and low blood pressure associated with symptoms of hypoglycaemic episodes. None of the immediate family members had diabetes nor had he himself ever taken any antidiabetic medications. The physical examination was normal with slightly raised BMI of 27. Blood workup showed inappropriately high insulin level (13.6 u IU /ml, and high C-peptide levels (1.74ng/ml) with low blood glucose level of 25mg/dl and good ACTH (74.7 normal range: <45) and cortisol response (28.97 ug/dl, normal range: 4.30-22.4) to stress. A hormonal profile for the possibility of Multiple endocrine neoplasia (MEN) type1 was conducted but investigations revealed negative results.

Department of Endocrinology, Shaukat Khanum Cancer Memorial Hospital and Research Centre, Lahore, Pakistan.

Correspondence: Wania Rafaey. **e-mail:** wania21@live.com

ORCID ID: 0009-0006-8359-8870

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Table:-1 Hormonal Profile for the possibility of Multiple Endocrine Neoplasia (MEN) 1 syndrome

Investigations	Patient's Value	Normal Range
Insulin	13.6 uIU/ml	Adult (fasting) up to 29.1
Glucose (Fasting)	25mg/dL	70-99
C- Peptide	1.74ng/mL	0.9-7.1
ACTH	74.7	<45.0
Cortisol	28.97	4.30-22.4
Serum calcium	9	8.5-10.5
Prolactin	15ng/ml	1.9-25

-ACTH: Adrenocorticotropic hormone
- C- peptide: Connecting peptide

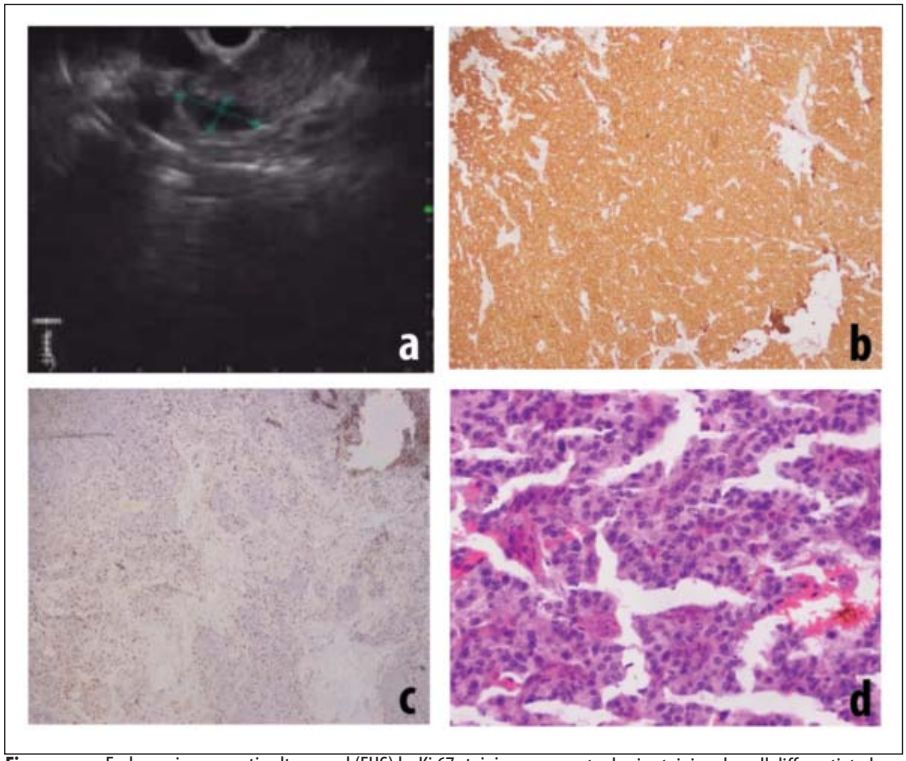

Figure: a- Endoscopic pancreatic ultrasound (EUS) b- Ki 67 staining, c- synaptophysin staining d- well differentiated neuroendocrine tumour

Imaging studies, including a CT abdomen with contrast, MRI abdomen with contrast and Ga68 DOTA positron emission tomography (PET scan) did not reveal any structural lesion. Endoscopic pancreatic ultrasound (EUS) was planned to localize the lesion as it has a higher sensitivity as compared to CT or MRI. The Endoscopic pancreatic ultrasound (EUS) showed a well- defined, ovoid mass measuring 19x8mm in the head of pancreas. (Figure: a) He underwent Whipple's procedure.

Histopathology showed well-differentiated neuroendocrine tumour (Figure b,c,d), WHO grade I, 1.7cm in size. Initially in the post- operative period he required small doses of insulin to control hyperglycaemia, now he is off insulin and doing well.

Discussion

An Insulinoma is a rare endocrine tumour of the pancreas that causes hypoglycaemia through its autonomous secretion of insulin. It is a very rare tumour with annual incidence of 0.7-4 per million person-year.[1] Insulinoma is usually a benign tumour, sporadic in origin and presents with a solitary small mass (< 2cm diameter). In 5-10% of the cases, insulinomas are multiple and associated with multiple endocrine neoplasia (MEN).[2] Symptoms of hypoglycaemia occur due to excessive production of insulin by abnormal proliferation of pancreatic beta-cells.[3] There is intermittent episodic secretion of insulin by the tumour that causes unprovoked hypoglycaemia. Symptoms of hypoglycaemia are both adrenergic and neuroglycopenic. Adrenergic symptoms include pallor, sweating, tremors and tachycardia. Neuroglycopenic symptoms develop due to lack of glucose in the brain cells and cause irritability, confusion, aggression, seizures and coma.[4] As a part of diagnostic workup, Whipple's triad should be confirmed, but it should be kept in mind that hypoglycaemia unawareness may develop later and confound the clinical picture.

The main factor in endogenous hyperinsulinism is the failure to suppress insulin secretion in the presence of low blood glucose levels. Hence, plasma insulin, C-peptide and proinsulin levels are inappropriately high with low blood glucose concentration. The gold standard test for biochemical diagnosis is 72 hours fasting during which plasma glucose, insulin, C-peptide and proinsulin are checked. This test can detect almost 99% of insulinomas.[5]

Insulinomas are found with equal frequency in the head, body and tail of pancreas. Early localization of the disease is essential to prevent fatal hypoglycaemia. Imaging techniques to localize the tumour include noninvasive and invasive modalities. Non-invasive techniques include trans-abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), with the sensitivity of CT and MRI approaching 70-85%.[6] Invasive modalities include endoscopic pancreatic ultrasonography (EUS), and intra-arterial calcium stimulation with hepatic venous sampling or angiography, and arterial stimulation venous

sampling (ARVS).[7] Endoscopic pancreatic ultrasonography has sensitivity of 70-95% and is the study of choice if non-invasive imaging modalities yield negative results. In this case, the biochemical workup was suggestive of pancreatic insulinoma but non-invasive imaging including CT abdomen, MRI abdomen with contrast and DOTA scan were negative for structural lesion. Therefore, endoscopic pancreatic ultrasound was done that showed an ovoid mass in the head of pancreas and resection of the tumour was planned. Diagnosis of this rare disease requires high index of suspicion based on clinical and laboratory findings and imaging techniques to localize the lesion. Surgery is often curative and is the standard of care to prevent fatal neurological deficit associated with prolonged hypoglycaemia[8]. Medical therapy with diazoxide, somatostatin analogues (octreotide, lanreotide, pasireotide) and evelorimus also helps to decrease insulin secretion in some cases.[9]

Conclusion

Diagnosis of this rare disease, pancreatic insulinoma requires high index of suspicion based on clinical and laboratory findings and imaging to localize the lesion. Endoscopic ultrasound (EUS) should be considered as imaging modality of choice in cases of difficult to localize biochemically proven Insulinomas. With early localization of structural lesion by using highly sensitive imaging modalities like EUS, severe life-threatening episodes of hypoglycaemia can be prevented by timely surgical removal.

Consent: Informed Consent taken from the patient for publishing his case.

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