International Journal on Gastroenterology and Liver Disorders

Asymptomatic Pancreatic Insulinoma without Typical Radiologic Features in a Young Woman: A Case Report

Case Report

Volume 3 Issue 1- 2023

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Article History

Received: March 6, 2023 Accepted: March 9, 2023 Published: March 10, 2023

Abstract

Background: Insulinoma is a rare neuroendocrine tumor.

Case presentation: MRI showed a 12-mm pancreatic area without specific NET features and Octreoscan was negative in a 18 years old female with asymptomatic hypoglycemia. EUS-guided FNB found a 12-mm hypoechoic lesion of the pancreatic head and histopathology confirmed NET-G2 diagnosis. After surgery diagnosis was confirmed and fasting glucose levels normalized.

Conclusion: Pancreatic insulinoma requires a stepwise challenging diagnosis.

Keywords: Insulinoma, EUS-guided FNB; Endogenous hyperinsulinemia hypoglycemia

Abbreviations: NET: neuroendocrine tumor; EUS: endoscopic ultrasound; FNA/B: fine needle aspiration/biopsy; ROSE: Rapid on-site Evaluation IHC: immunohistochemistry.

Introduction

Insulinoma is a rare neuroendocrine tumor with 3/1.000.000 annual incidence. Long-standing adrenergic and neuroglycopenic symptoms generally affect patients and asymptomatic presentation is very rare. Diagnosis is clinical: individuating fasting hypoglycemia with insulin inappropriately high value constitutes diagnostic pathway mainstay [1]. Especially in children and young adults other causes of endogenous hyperinsulinemic hypoglycemia maybe excluded, such as nesidioblastosis and insulin autoimmune syndrome [2]. Finding primary tumor is often challenging, but pancreas represents most frequent site, accounting for about 90% of cases [1].

Case Report

An eighteen-year-old woman found low plasma glucose levels (40mg/dl) in a routine blood test without hypoglycemia-related symptoms. She had no significant medical or pharmacological history. She had no family history of diabetes, thyroid or pituitary disease. She was referred to the Endocrinological Service of our institution.

Routine fasting blood tests confirmed hypoglycemia (64mg/dl) with apparently normal insulin and c-peptide levels (16.4mcUI/ml and 3.9ng/ml respectively). Chromogranin-A was in a normal range (34ng/ml) with slightly elevated NSE plasmatic level (13.25mcg/l – n.r. 0-12).

Low basal cortisole level (3.5mcg/dl – n.r. 6.7- 22.6) was also found and ACTH stimulation test was performed excluding Cushing Syndrome.

Abdomen MR was performed to detect suspected pancreatic lesion, such as insulinoma. MR imaging showed, at the pancreatic head, a focal area, 12.5 x 9.2mm in diameter, with moderate hyperintensity in T2-weighted and SPIR sequences, hypointensity in T1-weighted sequences and a restrictive pattern on DWI. Contrast-enhanced dynamic sequences did not show significant contrast enhancement in arterial or venous phases (Figure1). No abdominal lymphadenopathy or distant metastasis were detected. RM – cholangiography sequences were not included because claustrophobic attack.

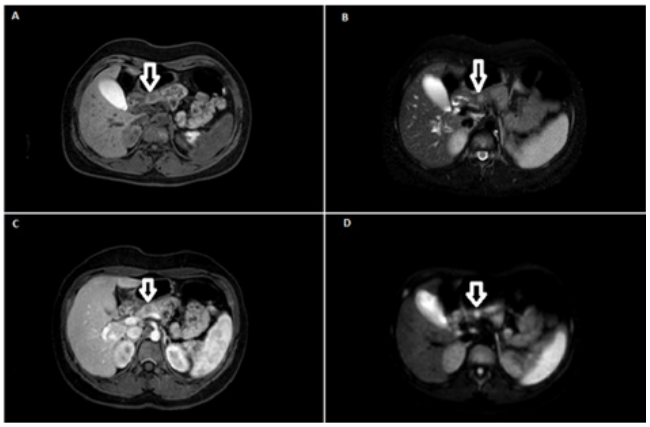

Figure 1: Contrast-enhanced MR imaging: centimetric focal pancreatic area with hypointensity in T1- weighted sequences (A), hyperintensity in T2-weighted sequences (B), hypoenhancement in arterial phase (C) and restrictive pattern in DWI sequences (D)(Arrows).

In order to assess the somatostatin receptor status confirming neuroendocrine tumor suspicion and eventually exclude distant metastasis, a 68Ga – labeled somatostatin analogs (DOTA-TOC) CT/PET was performed. This technique revealed a physiological marker accumulation in the pancreatic uncinate process without pathological accumulation areas with somatostatin type 2,3 and 5 receptor overexpression.

EUS with linear probe (GF-UCT180 - Olympus, Tokyo, Japan) was performed and a hypoechoic 11 -mm lesion, round with definite edge and small internal calcification, was confirmed in pancreatic head (Figure 2). Biopsy sampling was performed by 22 Gauge lancet needle type FNA device (Echotip Ultra – Cook Medical), (1 pass), by 22 Gauge lancet needle type FNB device (Echotip Procore- Cook Medical) (1 pass), and by 22 Gauge Franseen needle type FNB device (Acquire – Boston Scientific) (2 passes), obtaining sufficient tissue for pathology and cytology. Adequacy of specimens was confirmed by gross visualization by pathologist (ROSE).

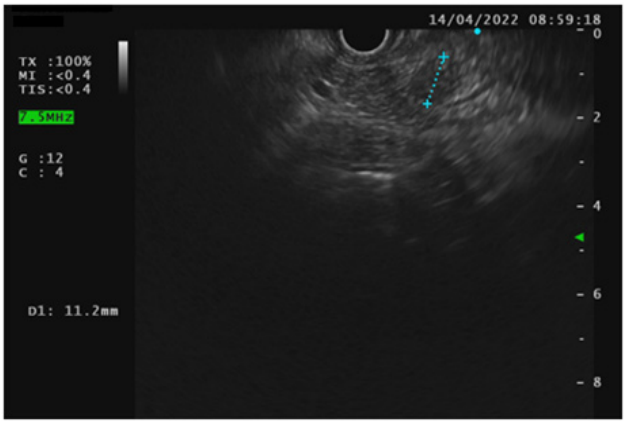

Figure 2: EUS imaging: small 11-mm round ipoechoic lesion in pancreatic head. Surrounding pancreatic parenchyma appears normal.

Histopathological evaluation revealed little tissue fragments composed by cells with round nucleus and eosinophilic cytoplasm. IHC was positive for chromogranin and INSM-1 and negative for insulin (Figure 3). Proliferation index (ki-67) was 4%. All these findings were suggestive for neuroendocrine pancreatic tumor (G2).

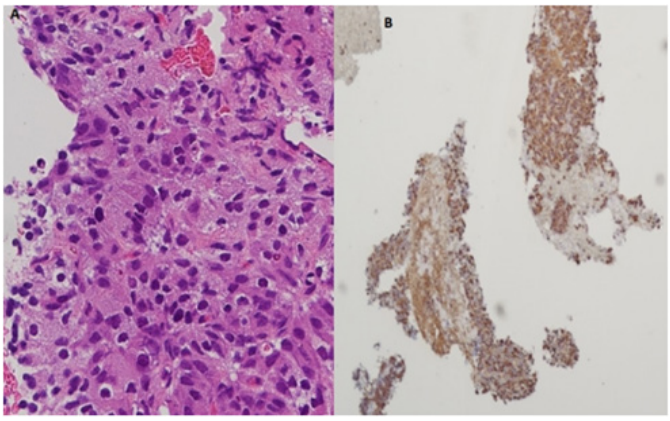

Figure 3: Histopathological examination showed cells with round nucleus and eosinophilic cytoplasm (Hematoxylin & Eosin stain) (A) and positive IHC for chromogranin (B).

In order to differentiate between non-secerning neuroendocrine pancreatic tumor with otherwise-explainable hypoglycemia and pancreatic insulinoma, a fasting glucose test was initiated at 6.00 am after light meal. After 6 hours fasting glucose level was 68mg/dl, with insulin and c-peptide blood levels respectively 10.2mcU/ml and 2.6ng/ml. About 5 hours late patient developed dizziness and asthenia and glucose, insulin and c-peptide blood levels were respectively 36mg/dl, 13,7mcUI/ml and 2.8ng/ml. Owing to symptoms appearance and insulin and c-peptide increase despite lowering glycemia, fasting test was interrupted and considered positive. One month later a pylorus-preserving duodenocephalopancreasectomy was performed without post-operative complications. Surgical specimen pathology assessment confirmed diagnosis and six months after surgical treatment patients remains asymptomatic and blood glucose levels are persistently in normal range.

Discussion

In our case MR scan posed initial suspicion, finding a small pancreatic area, without typical neuroendocrine tumors arterial contrast enhancement and following slow wash-out. T1 weighted hypointensity, T2- weighted hyperintensity and restrictive pattern on DWI were compatible with solid lesion but not definitely conclusive. MR sensitivity in detecting pancreatic NETs is 79% (M.R. 54-100) with a high specificity (around 100%) [3], but atypical contrast features are not uncommon especially in insulinomas and should require further diagnostic evaluation [4,5].

CT has a good sensibility (67-94% - M.R. 82 %) and an optimal specificity (96%) in individuating pancreatic insulinomas, because of frequent typical contrast enhancement features, such as contrast enhancement in arterial and portal phase, with higher attenuation than surrounding pancreatic parenchyma in venous phase, in spite of small dimensions [3]. Radiation exposure, especially in young patients, may be a concern.

Considering insulinomas elective pancreatic localization and better spatial resolution than CT or RM scan, EUS represents, in spite of comparable sensitivity rate (57 -100%, M.R 86%) [3], an essential diagnostic tool when insulinoma is suspected and target lesion needs to be found. In fact, EUS seems to be superior than CT and MR in detecting pancreatic neuroendocrine tumors and also insulinomas considered alone, with a similar detection rate (86%) [6-15]. A recent metanalysis

confirmed that EUS was associated with high diagnostic value for insulinomas localization, with 81% and 90% in sensitivity and specificity respectively [16]. Pancreatic neuroendocrine tumors typically appear as vascular, hypoechoic lesions, with a smooth margin and homogeneous echogenicity, with a cystic component in 22% of cases without obstruction of the main pancreatic duct [17].

Pathological assessment in FNA/B tissue sampling is also challenging, considering possible histological sample scarcity and sensible insulinoma markers lacking, as insulin positive immunohistochemistry may be absent in 20% of cases [18]. Chromogranin and INSM-1 are considered neuroendocrine non-specific markers [19]. FNB sampling seems to be superior than FNA in predicting pancreatic NET grading, obtaining more frequently adequate pathological material and showing better correlation of ki-67 index with surgical resection histology [20]. EUS-guided FNA/B achieves sensitivity up to 94% and specificity up to 95% for insulinoma diagnosis [1]. Radiation and contrast sparing, diagnostic accuracy and tissue sampling possibility may overcome high costs, invasiveness and complications risk.

68Ga – labeled somatostatin analogs (DOTA-TOC) CT/PET (Octreoscan) has low sensibility (25%) in detecting insulinomas owing to sst2 and sst5 low level expression [21]. Specificity is also sub-optimal, considering physiological marker hyperaccumulation in the uncinate process [22], such as depicted in our case.

Conclusions

In our opinion, such as depicted in clinical case, insulinoma diagnosis is mainly clinical, with a first challenge to correlate frequent non -specific symptoms with insulinoma, and a following challenge to find tumor localization. In the latter situation we believe that EUS represents an essential diagnostic tool. EUS-guided FNB is the choice technique in tissue sampling and grading prediction. Considering elevated frequency of pancreatic small incidentalomas, often represented by non-secerning neuroendocrine tumors [23], and difficult insulinoma pre-operatory histological assessment, only symptoms disappearance and persistently normal blood glucose levels after tumor removal could confirm diagnosis definitively and exclude other rarer endogenous hyperinsulinemic hypoglycemia causes.

Conflict of interest

None declared.

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