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Case report

Insulinoma - The Approach to the Diagnosis, Based on a Case Report

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Abstract

Insulinoma is the most common cause of endogenous hyperinsulinism. Most are benign and solitary. Hereby the authors present a 36-year-old woman who was admitted for confusion, aggressive behaviour, and visual hallucinations. Initial investigation revealed hypoglycaemia, and the patient recovered after the administration of intravenous glucose. The 72-hour fasting test was compatible with hyperinsulinism. Endoscopic ultrasound detected a nodule in the tail of the pancreas. Surgical resection of the nodule was performed, and histological examination revealed a pancreatic neuroendocrine tumour. The patient had a favourable outcome with resolution of the symptoms.

Keywords: ***Hyperinsulinism, hypoglycaemia, insulinoma, neuroendocrine tumor***

Introduction

Insulinoma belongs to the group of functional neuroendocrine tumours and is the most common cause of endogenous hyperinsulinism. Its aetiology is not fully understood- in most cases, it is benign and solitary, but up to 10 per cent are malignant, multiple and can metastase to the liver and retroperitoneal lymph nodes [1]. Insulinomas may also be associated with multiple endocrine neoplasms. There is twice the incidence on women than men, usually in the 5th decade of life.

This case report highlights the importance of a holistic approach to the patient- symptoms of hypoglycaemia and neuroglycopenia can be confused with psychiatric disorders, and hypoglycaemia is uncommon in patients who are not treated with oral antidiabetic agents or insulin. Insulinoma is a rare entity- its incidence is up to four cases per million per year [2]. On average, insulinomas take 18 months to be diagnosed from the start of symptoms [3].

Case report

A 36-year-old Caucasian woman presented at the emergency department for altered mental status, disoriented, with aggressive behaviour and visual hallucinations. Physical examination was otherwise normal, particularly the neurological examination, which did not reveal any other signs besides those described at admission. The initial assessment identified hypoglycaemia 28mg/dL and the patient recovered immediately after administration of intravenous glucose, with adequate behaviour. Her family mentioned three previous episodes of confusion after a long period of fasting and denied any history of psychiatric disorders, alcohol misuse, regular medication, or recreational drugs. There was no relevant familiar history beyond cardiovascular diseases. Laboratory work revealed only hypoglycaemia and there were no drugs presented in blood or urine samples, mainly cocaine, cannabinoids, and opiates. Brain computed tomography (CT) did not reveal any structural lesions.

The patient was admitted to the Internal Medicine ward for further study of hypoglycaemia. She was submitted to the 72-hour fasting test, which was interrupted 14 hours after due to blood glycaemia of 32mg/dL, together with adrenal symptoms, elevated C-peptide and high insulin levels (Table 1). Cortisol levels and serum calcium were in the reference range, and screening for sulphonylurea was negative. The results favoured endogenous hyperinsulinism, being insulinomas the most frequent cause. Anti-insulin and anti-insulin receptor autoantibodies were also negative.

Contrast-enhanced abdominal CT and gadolinium-enhanced abdominal magnetic resonance imaging (MRI) did not reveal any pancreatic lesions. For preoperative lesion assessment, endoscopic ultrasound (EUS) successfully detected a 17,3x10,1 mm encapsulated nodule in the tail of the pancreas (Fig. 1). Histological examination after a fine needle aspiration revealed aspects compatible with a well-differentiated neuroendocrine tumour.

The patient was submitted to laparoscopic distal pancreatectomy without major complications. Histological examination of the surgical specimen revealed positive chromogranin A and synaptophysin markers in immunohistochemical analysis, with Ki-67 index lower than 2% (Fig. 2), confirming a functional pancreatic neuroendocrine tumour (F-PNET) G1.

The follow-up surveillance (nowadays two years after the diagnosis) did not show new lesions by imaging control nor recurrence of symptoms suggesting hypoglycaemia.

Table 1: The 72-hour fasting test, interrupted 14 hours later for symptomatic hypoglycaemia

	1st hour	14 hours	Reference values
Glycaemia (mg/dL)	73	32	70-100
C-peptide (ng/mL)	6,86	4,87	0,9-4
Pro-insulin (pmol/L)	81	72	< 5
Insulin (µU/mL)	22	16	< 3
β-hydroxybutyrate (mmol/L)	0,01	0,02	> 2,7
Sulphonylurea	Negative	-	-

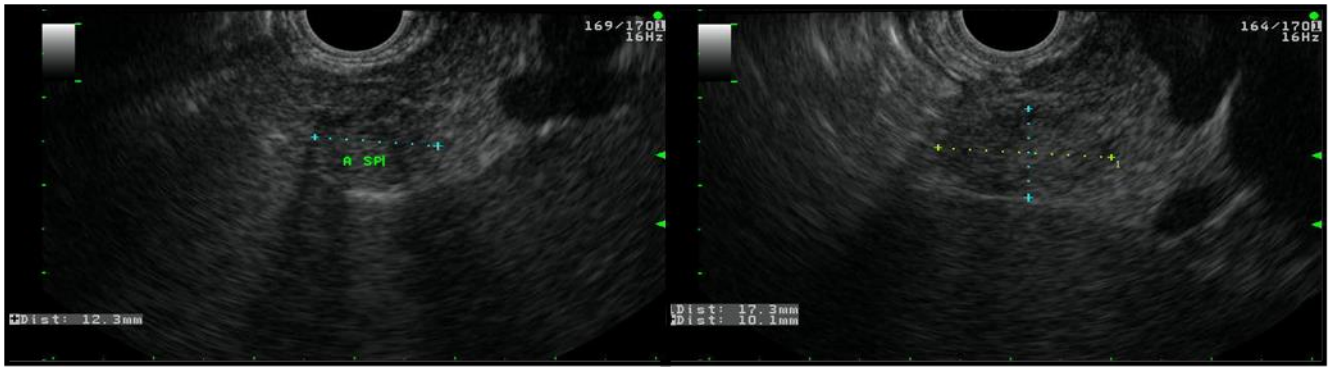
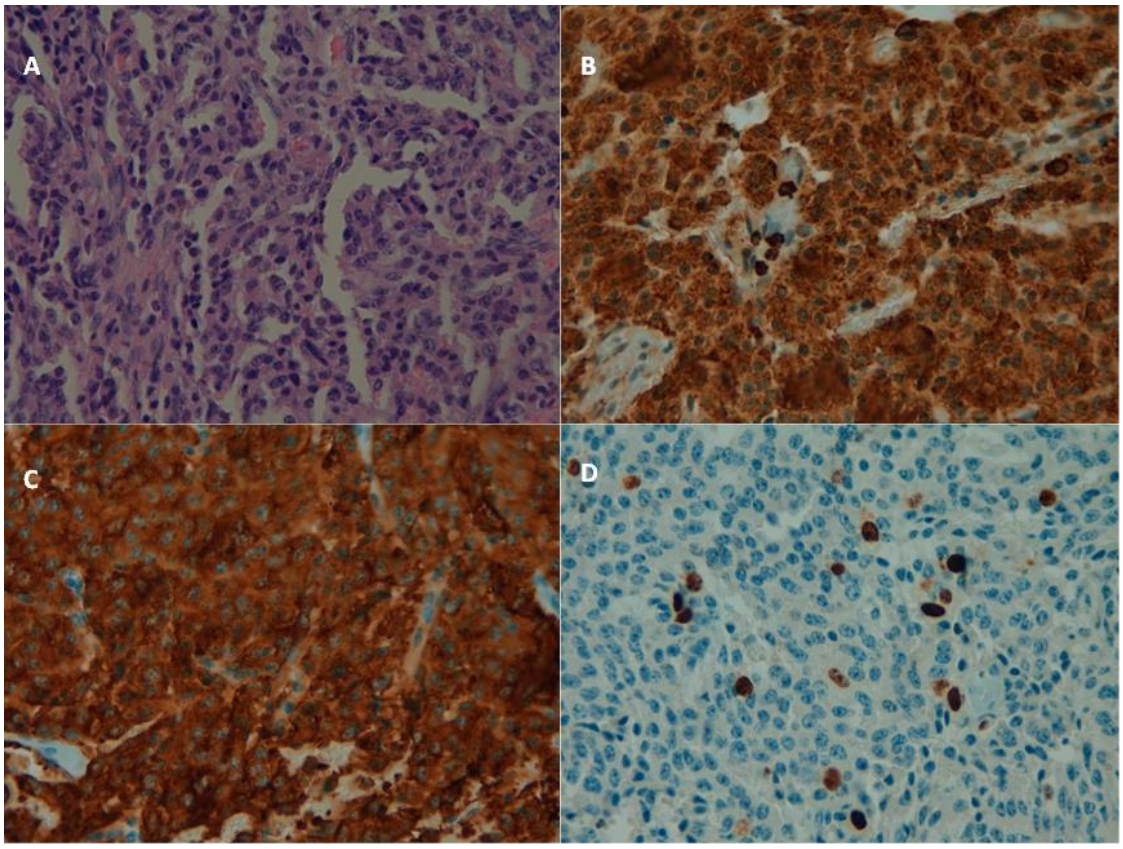


Figure 1: Endoscopic ultrasound, revealing a nodule in the tail of pancreas

Figure 2: Histopathological evaluation of the pancreatic surgical specimen: A- haematoxylin-eosin staining showing aspects compatible with well-differentiated neuroendocrine tumor; B- Immunohistochemistry studies- tumor cells staining for chromogranin A; C- Immunohistochemistry studies- tumor cells staining for synaptophysin; D- tumour cells' Ki-67 index lower than 2%.



Discussion

Reported low plasma glucose levels are necessary but insufficient to raise suspicion of a hypoglycaemic disorder. Only in the presence of the Whipple's triad (documented hypoglycaemia, especially if fasting; symptoms of hypoglycaemia; and relief of symptoms after glucose administration) may one make that assumption. The most frequent symptoms are associated with neuroglycopenia- headaches, visual disturbances and behavioural changes are the most common. Symptoms due to adrenergic stimulation secondary to hypoglycaemia are also frequent, including palpitations, sweating and tremors.

Hyperinsulinism is confirmed by the prolonged fasting test (normally 72 hours), which remains the gold standard diagnostic test. The presence of symptoms of hypoglycaemia, measurement of fasting glycemia <40 mg/dL, insulin level >3 µU/mL, C-peptide level ≥0,9 ng/mL and proinsulin >5 pmol/L highly suggests hypoglycaemia due to hyperinsulinism. Literature reports that in the majority of patients hypoglycaemia will surge before 72 hours; therefore many authors have proposed shortening the prolonged

fasting test to 48 hours [4]. In this case report, the patient took only 14 hours to develop hypoglycaemia together with neuroglycopenic symptoms, which favours this change in the approach to the diagnosis.

Nearly 100% of insulinomas are localized in the pancreas [5]. Determining its localization is extremely important for surgical approach. Although contrast-enhanced CT scan constitutes the first imaging method due to its wide availability, MRI is preferred for visualizing the pancreas and the liver. EUS is the best imaging method to identify pancreatic neuroendocrine tumours, with sensitivity rates of 82-93%. It is thus recommended if other non-invasive imaging tests are non-conclusive [6]. Moreover, it allows for biopsy and diagnostic confirmation in preoperative management. 68Ga/64Cu-DOTA-somatostatin analog positron emission tomography (PET) in combination with CT is also recommended for diagnosing insulinomas and allows the identification of lymph node, bone or liver metastasis [7]. Considering this patient's case, EUS was available at the Hospital and provided the accurate location of the pancreatic insulinoma, after CT and MRI were inconclusive.

If imaging methods fail to localize neuroendocrine tumours, physicians may consider other aetiologies like nesidioblastosis and autoimmune hypoglycaemia, far less common than insulinomas.

Validation by histological examination is mandatory- the immunohistochemical detection of synaptophysin and chromogranin A proves the phenotype a neuroendocrine tumour. It is also important to detect the number of mitotic figures to determine the Ki-67 index to assess the tumour's grading.

In benign, solitary lesions, surgical resection is the indicated treatment and is associated with favourable outcomes. The first follow-up should take place six months after surgery, with imaging control by CT scan, MRI or PET-CT.

Conclusion

Insulinoma is a rare entity and its diagnosis can be challenging. Clinical presentation might resemble psychiatric disorders, and its localization is often difficult to determine. Physicians must have a high index of suspicion and the approach should be multidisciplinary, including Internists, Oncologists, Endocrinologists and Surgeons. The prognosis is usually good.

Ethics approval and consent to participate

Not applicable

List of abbreviations

CT- Computed tomography
EUS- Endoscopic ultrasound
F-PNET- Functional pancreatic neuroendocrine tumour
MRI- Magnetic resonance imaging
PET- Positron emission tomography

Data Availability

Not applicable

Conflicts of interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Author's contributions

CCP was responsible for research design, data collection, drafting of the paper and spelling revision. RAP and AE were responsible for data collection. CA was responsible for histopathologic evaluation of pancreatic surgical specimen and pictures. HJC, BNB and MP were responsible for revision.

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