Insulinoma: A case report and literature review

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Abstract

Insulinoma is a rare endocrine tumour of the pancreas derived from ß cells that ectopically secrets insulin, which results in hypoglycaemia. The average age of occurrence is 40 to 50 years old. The most common symptoms are caused to the effect of the hypoglycaemia on the central nervous system.

Insulinomas are generally small (≥90% are ≤2 cm), usually not multiple (90%), and only 5 to 15% are malignant. They almost invariably occur in the pancreas, distributed equally in the pancreatic head, body and tail.

Diagnosis relies on clinical features, along with laboratory tests and imaging investigations to aid localization.

We report a case of a 57 year old man with episodes of neuroglycopenia, manifested by dizziness, sweating, headache and confusion, since the age of 50 years. A 72 h fast test, serum insulin levels and C-peptide strongly suggested insulinoma.

Preoperative tumour localization was performed by MRI and selective angiography, revealing a 2 cm nodule in the tail of the pancreas; ultrasonography (US), computed tomography and Octreoscan were not helpful.

Surgical resection was performed, and the splenic vein blood sample showed insulin levels of 5410 mcUI/ml and 186 mcUI/ml respectively, before and after tumour extraction.

Histopathology was consistent with the diagnosis of benign Insulinoma.

There was favourable clinical evolution, with complete normalization of the clinical symptoms and laboratory results.

Key words: Insulinoma, hypoglycaemia.

INTRODUCTION

Insulinoma, or beta cell tumour of the pancreas, is characterized by the appearance of signs and symptoms resulting from hypoglycaemia secondary to hypersecretion of non-controlled insulin.[1] Whipple's triad is typical: hypoglycaemia induced by fasting glycaemia <45 mg/dl and rapid resolution of complaints through the administration of glucose.[1] Its incidence is about ten cases per million inhabitants.[2] Outpatient follow-up with other specialties is customary, before making a definite diagnostic.

CLINICAL CASE

57-year old male, with unquantified smoking and drinking habits. Patient reported episodes of memory loss, disorientation, bizarre behaviour, sweating, tremors and generalized seizures for the past seven years, for which reason an Electroencephalogram and cranioencephalic Computed Tomography and Magnetic Resonance Imaging were performed, all of which were normal. Diphenylhydantoin was commenced, without clinical improvement. Due to alterations in the hepatic function tests in the routine analyses, he was referred to the Gastroenterology service of our Hospital, where a fasting glycaemia of 40 mg/dl was detected. He was admitted to the Medicine service II for hypoglycaemic etiologic investigation.

Physical examination showed no significant changes, and the neurological examination was normal. During hospitalization, multiple episodes of hypoglycaemia were noted.

The laboratory study highlights:

- Hemogram, renal function, thyroid function, ionogram, cortisol and pituitary hormones within the normal laboratory values;
- AST/ALT 29/45 U/L; AF 97 U/L; G-GT 283 U/L;
- Gastrin 76 pg/ml, calcitonin 15 pg/mL and thyroglobulin 5.9 ng/mL;

The 72-hour fasting test was conducted, showing

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TABLE I

Prolonged fasting test

Time	Glycaemia mg/dL (≥ 40 mg/dL)	Insulinemia µU/mL (≤ 6 µU/mL)	C-peptide ng/mL (≤ 0.9 ng/mL)	Insul/glyco (< 0.3)
9:30am	101	4.8	1.5	0.047
10:30am	62	19.3	3.4	0.31
1:30pm	38	46.5	4.4	1.20

insulin and C-peptide levels suggestive of Insulinoma *(Table I)*.

Other causes of fasting hypoglycaemia were excluded, namely the administration of exogenous insulin and/or drugs, ingestion of sulfonylurea, or tumours secreting "insulin-like" growth factors.

Ultrasound, abdominal CT scan and scintigraphy with Octreoscan were inconclusive. MRI and abdominal CT angiography *(Fig. 1 and 2)* showed a nodular formation of approximately 2 cm in diameter in the pancreatic tail. Arteriography of the celiac trunk revealed a vascularised nodule in the pancreatic tail *(Fig. 3)*.

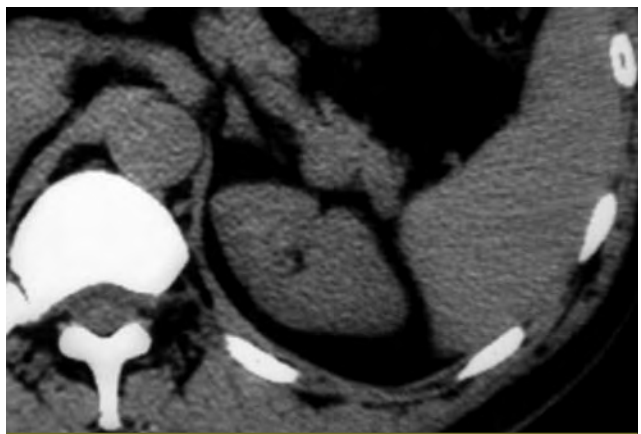
The patient was submitted to pancreatojejunostomy (enucleation and excision of the tumour), with intraoperative localization by palpation and ultrasonography *(Fig. 4)*. The insulin in the pre-resection splenic vein blood sample was 5410 mcUl/ml and after resection, 186 mcUl/ml. The postoperative period progressed uneventfully.

Histological diagnosis of benign insulinoma of the pancreatic tail was performed *(Fig. 5, 6 and 7)*, with favourable clinical progress and normal of the symptoms and laboratory tests.

DISCUSSION

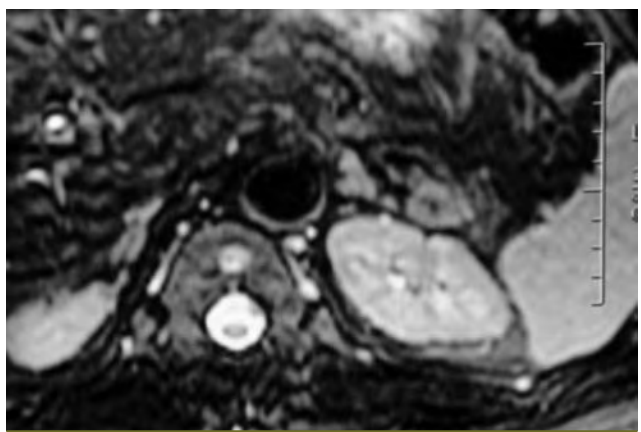
The pancreatic tumours of β cells cause hypoglycaemia, which may be symptomatic through the uncontrolled hypersecretion of insulin. The most common tumours are gastrinomas, followed by insulinomas.[3]

Insulinoma is a rare neuroendocrine tumour (4 cases/1,000,000/per year), generally with intrapancreatic location, with an average age of onset of 47 years and affecting predominantly females (1.4:1).[4] The lesions usually appear in isolation, but may be multiple in 10% of cases.[2] The lesions are small, with a diameter of less than 2 cm in 90% of cases and 1.3 cm in 50% of cases.[4] Most are benign. The malignant form, with dissemination to local lymph or liver nodes, occurs in only 10% .[4] Insulinoma may be compared with the Multiple Endocrine Neoplasia (MEN I) in 7.6% of cases or Wermer's syndrome (hyperparathyroidism, cell tumour of the pancreas and pituitary tumour).[5] After successful surgical excision, the ten-year survival rate is 88%, with a high risk of recurrence in patients with MEN-1.[4]



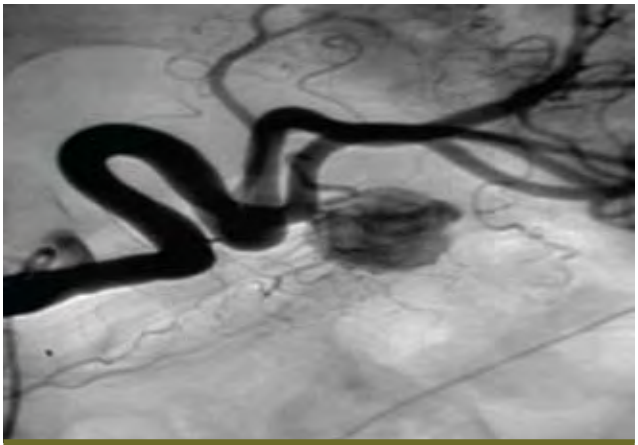
Nodule in the posterior face of pancreatic tail.

FIG. 1



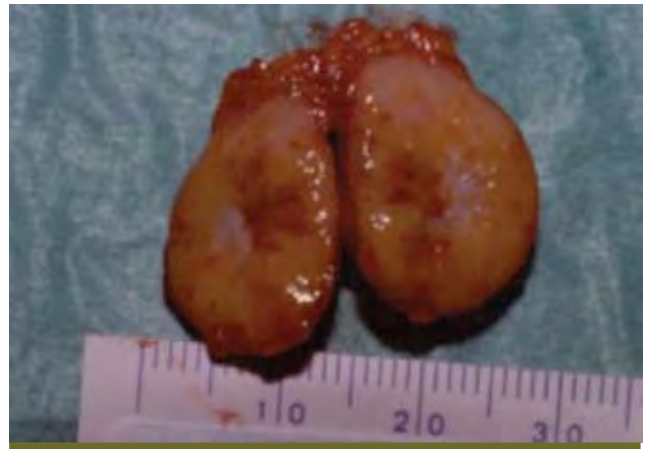
NMR definition of pancreatic nodule.

FIG. 2



Selective arteriography of splenic artery showing tumor vascularization.

FIG. 3



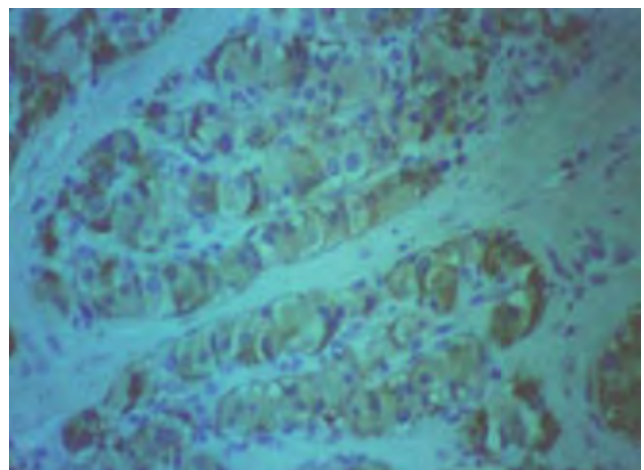
Macroscopic appearance of the nodule.

FIG. 4

The symptoms, a consequence of secondary hypoglycaemia to uncontrolled and excessive secretion of insulin, can be divided into two categories: neuroglycopenic (behavioural changes, mental confusion, visual changes, fatigue, convulsions and loss of consciousness) and neurogenic (hunger, sweating, paresthesia, anxiety, tremors, palpitations), with a clear predominance of the first group. Patients with insulinoma often have other previous diagnoses, especially neurological (epilepsy, etc.) and/or psychiatric, occurring, on average two, years between the onset of clinical manifestations and the exact diagnosis.[6]

This diagnosis is suggested by Whipple's triad (hypoglycaemia induced by fasting with glycaemia <45 mg/dl and rapid resolution of the complaints through the administration of glucose), and is confirmed in 98% of the cases by fasting test (in hospital, with repeated doses of glucose and insulin up to 72h)[2] *(Table II)*. The investigation must also consider the possibility of secondary hypoglycaemia to an alteration in the hypothalamus-hypophysis-suprarenal axis (hypopituitarism, Addison's disease), administration of exogenous insulin, drugs (sulfonylurea, alcohol, pentamidine, quinidine, propranolol, haloperidol, salicylates, sulphonamides), critical clinical situations (sepsis, severe hepatic failure, cirrhosis, renal failure, CHF, shock) .[7]

Locating the tumor is critical; this is done by imaging techniques combined with selective dosages, which currently enable 90% of cases to be identified *(Table III)*. The recommended localisation technique

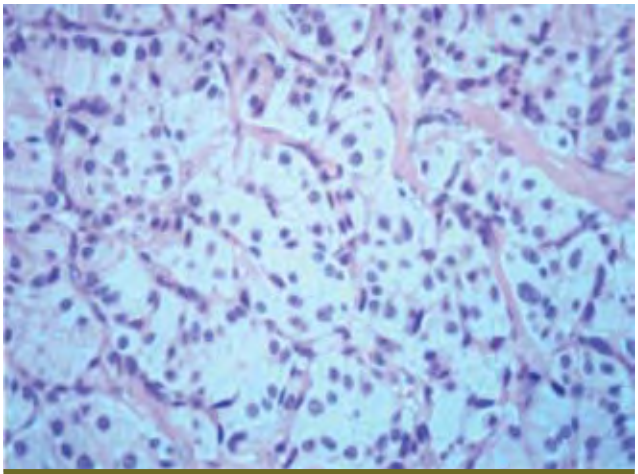


Optical microscopy image - immunohistochemistry technique with anti-Ac-insulin marked with peroxidase, revealing intracytoplasmic granules in the β cells, containing insulin.

FIG. 5

currently recommended is high-resolution CT, leaving the preoperative Echo-endoscopy in reserve for insulinomas of the proximal pancreas. Other imaging methods are reserved for situations in which CT is inconclusive. The assessment of preoperative imaging combined with intraoperative ultrasound identifies the exact location of these tumours in more than 95% of patients.[6]

Recession surgery (laparoscopy or laparotomy) is the preferred treatment and is usually curative. Since most of these tumours are benign, the rate of cure is approximately 75-98%, with prognosis depending on



Optical microscopy image - β cells with ovoid nucleus and eosinophilic cytoplasm, with no mitoses, grouped into trabeculae.

FIG. 6

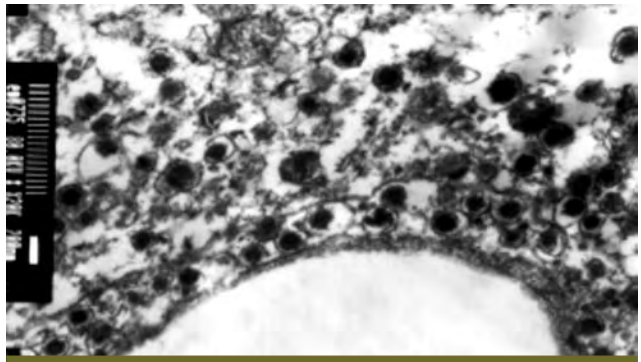
TABLE II

Diagnostic criteria of insulinoma after 72 hrs fasting

Dosage	Concentration
Glycaemia (≥ 40 mg/dL)	≤ 45 mg/dL
Insulin (< 6 µU/mL)	≥ 6 µU/mL
Plasma C-peptide (<0.2 mmol/L)	≥ 0.2 mmol/L
Proinsulin (≤ 20% of total insulin)	≥ 30% of the amount of insulin after nocturnal fasting
Plasma sulfonylurea	Negative
Plasma beta-hydroxybutyrate (> 2.7 mmol/L)	≤ 2.7 mmol/L
Alteration of glucose with 1 mg glucagon administered (<25 mg/dl)	≥ 25 mg/dl every 30 minutes

the level of presentation and/or with recession was completely achieved.[6]

Several techniques may be used, depending on the size and location of the lesion - enucleation, distal pancreatectomy, pancreaticoduodenectomy, partial pancreatectomy. Laparoscopic enucleation is currently the preferred method.[6] Medical treatment (diazoxide, supplemented by octreotide and corticosteroids) is intended only in cases of hidden insulinoma or as a palliative measure in inoperable patients.[8] ■



Electronic microscopy - β cells with granules containing insulin.

FIG. 7

TABLE III

Relationship between the imaging technique and the % of diagnostic sensitivity of insulinoma.

Imaging Techniques	Diagnostic sensitivity
Abdominal ECO/CT/ MRI	17-64%
Scintigraphy with Octreoscan	↓
Preoperative echo-endoscopy	80-85% (head and body)
Selective catheterization of the portal vein with doses	75%
Selective arteriography of the celiac trunk and its branches with doses	90%
Intraoperative pancreatic ultrasonography	≥ 90%

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