

Diagnostic Features of Benign Pancreatic Insulinomas. An Analysis of Three Cases

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Abstract

Insulinoma is a neuroendocrine tumour deriving mainly from the pancreatic islet cells that produces excessive amounts of insulin. Accurate preoperative detection and localization of insulinoma is essential for the selection of appropriate candidates for surgery. We present the case reports of three patients with benign pancreatic insulinoma. Preoperative assessment was performed by using transabdominal ultrasonography, computed tomography and magnetic resonance imaging. Their performances for the effectiveness in detecting and localizing benign insulinoma were compared. We concluded that an appropriate preoperative imaging assessment was in our case impossible, intraoperative inspection and palpation of the pancreas still being superior.

Key words

Neuroendocrine tumor - insulinoma - hypoglycaemia - imaging diagnosis

Rezumat

Insulinomul benign pancreatic este o tumoră neuroendocrină ce derivă din celulele pancreatice și produce o cantitate crescută de insulină. Diagnosticul precis și stabilirea cu acuratețe a localizării insulinomelor este esențială în elaborarea protocolului operator. Prezentăm trei pacienți diagnosticați cu insulinom benign pancreatic. Evaluarea imagistică pre-operatorie a fost efectuată prin ecografie pancreatică trans-abdominală și intraabdominală, tomografie computerizată și rezonanță magnetică nucleară. Am evaluat comparativ acurațea detecției localizării insulinomelor pancreatice prin tehnici imagistice și metode clasice de diagnostic clinic. Am constatat că, adesea, diagnosticul

imagistic în acest tip de tumori este neconcludent, evaluarea preoperatorie prin examen clinic și probe paraclinice de laborator fiind mai eficientă.

Introduction

Insulinoma is a neuroendocrine tumour derived mainly from the pancreatic islet cells producing excessive amounts of insulin. The tumour can continuously discharge small amounts of insulin, producing fluctuation of insulin blood level (1). Insulinomas are the most frequent cause of hypoglycaemia due to an endogen hyperinsulinism (2). Ten percent of insulinomas are malignant, of which 10% are multiple, especially in patients with type 1 multiple endocrine neoplasia (MEN1).

The clinical diagnosis of insulinoma is based on the Whipple triad (3) which is present in 75% of the patients: episodic hypoglycaemia, hypoglycaemia during fasting with values <50 mg/dl and the spectacular reversal of the central nervous manifestations after glucose administration. Symptoms due to the local effects of the tumour mass are extremely rare (4). In the past the diagnosis could not be established or it was delayed. Often the patients presented multiple admissions in psychiatric clinics being treated for psychomotor epilepsy and psychotic syndromes.

Case reports

Three patients were diagnosed in our department with benign pancreatic insulinoma, two women and one man aged between 28 and 70. Over the last two years the pre-surgical imaging evaluation was performed in accordance with the international standard. The assessment of serum insulin level was performed by an immunoassay method. C-peptide suppression test was performed. After an overnight fast, the patients received an infusion of insulin (0.125 U/kg) over 60 minutes. Blood specimens were collected immediately prior to the infusion, then every 30 minutes for two hours. The patients with insulinoma failed to suppress C peptide to normal levels. Glucose (spectrophotometry) and C-peptide analyses (immunoassay) were performed.

Significant hypoglycaemia appeared during testing, requiring continuous medical monitoring. Our patients will be briefly presented below.

Case 1

A 44 year old male patient was hospitalized for refractory hypoglycaemia crises having associated obesity. At the first admission (1994) the biochemical investigations showed extremely low levels of serum glucose, 24- 45 mg/dl, the transabdominal US showing in the head of pancreas a well delineated tumor with a diameter of 1.5 cm. The tumour was surgically enucleated. After surgery, hypoglycaemic crises occurring after 72 hours. A year later, the patient was admitted again, the transabdominal US and the CT scan showing other well delineated tumours in the head of pancreas. Limited pancreatic resections were performed, followed by a temporary improvement of the symptomatology. In 1997, the patient was hospitalized for hypoglycaemic crises refractory to treatment. The CT scan showed a new tumor (15/20/15 mm) in the head of pancreas, homogeneous, hyperdense in the arterial phase of the examination. After surgery, the patient developed acute severe pancreatitis, complicated with pancreatic abscess. The abscess was drained and under treatment with antibiotics, NSAIDS and octreotide, the evolution was slowly favourable. At discharge, the patient had normal

glycaemia. Later on, in 2003, due to the same clinical symptoms, a new CT scan showed in the pancreatic uncinata process a 2.5 cm nodule, in contact with the inferior vena cava. The MRI scan showed hyposignal areas (3-4 mm) in the body of pancreas, suggestive for adenomatous pancreatic hyperplasia. The tumour was surgically removed, but the result of the biopsy was uncertain. In 2004, the patient returned for re-evaluation. Blood was sampled for glucose and insulin levels every 4-6 hours and during hypoglycaemia symptoms. Glycaemia levels varied between 35-40 mg/dl and 136 mg/dl, concurrent serum insulin levels being 13-25 mU/ml. The diagnosis of insulinoma was additionally supported by insulin-to-glucose ratios, at different times during the monitored fast the ratio being about 0.36. C-peptide levels were exceeding 2.9 (± 2) ng/ml.

Angiography of the superior mesenteric artery showed a hypervascularized nodule (nutritive vessels coming from the inferior pancreatic-duodenal artery) with a diameter of 1.5 cm at early arterial stage. After subtotal pancreatectomy and splenectomy the patient evolution was favourable. The patient was discharged with normal glycaemia. The histological examination indicated nesidioblastoma.

Case 2

A 28 year old female patient was admitted to our clinic for neurological symptomatology and refractory hypo-

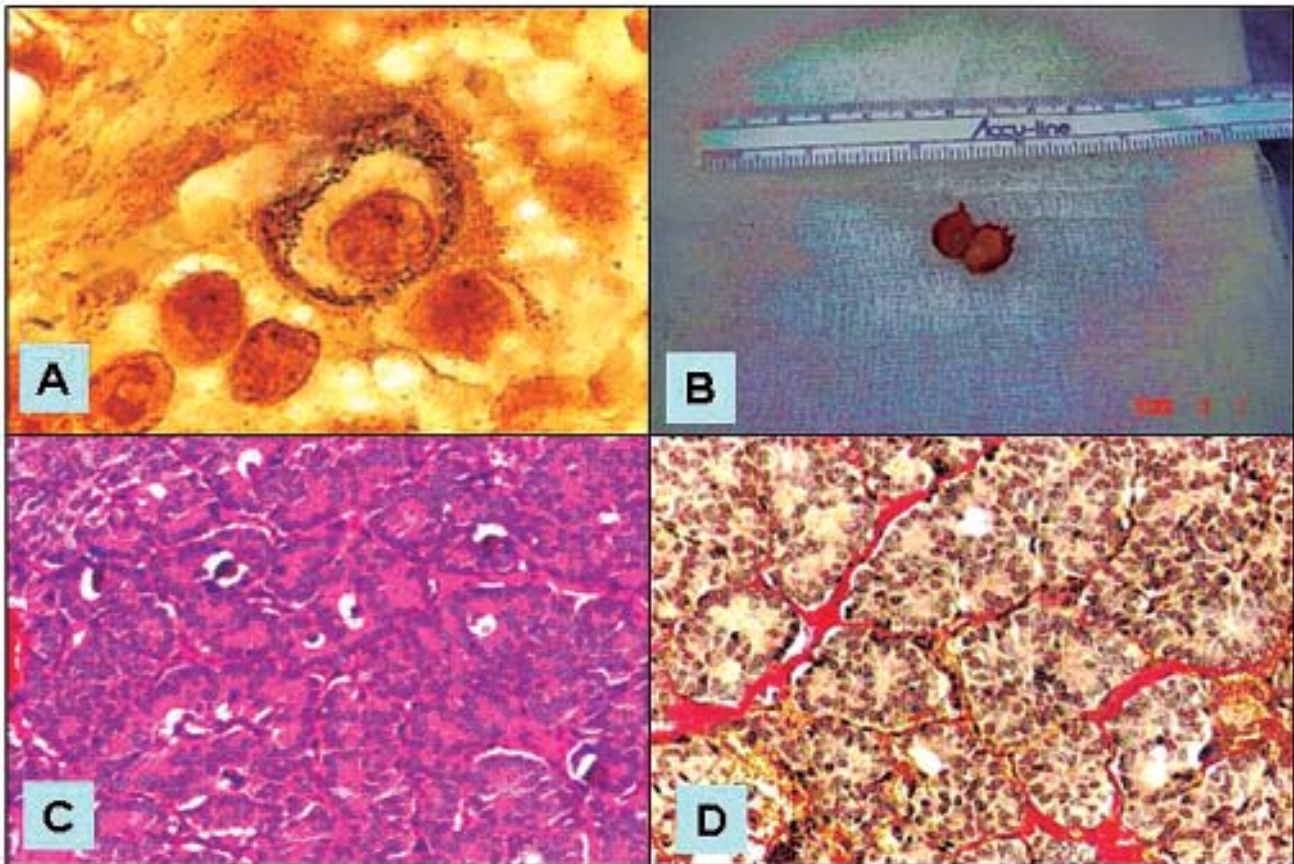


Fig.1 Microscopic aspect. Grimelius coloration, immersion, endocrine intracytoplasmic granulations, characteristic for insulinomas (A). **Macroscopic aspect:** benign, perfectly encapsulated insulinoma (B). **Microscopic investigation:** HE coloration (x10), trabecular and tubular architecture, psamomas, specific for somatostatinomas but also encountered in insulinomas (C). Van Gieson coloration (x10), insulinoma trabecular architecture, collagen fibres (in red) (D).

glycaemia. Due to the ambiguity of the symptoms, the patient had several admissions to a psychiatric clinic, where the diagnosis was delayed. The low glycaemia values raised the suspicion of insulinoma. The MRI scan revealed a pancreas normal in structure and dimensions, the tail region presenting an 8-10 mm area with vessels arranged circularly. The arteriography of the celiac trunk and the emerging arteries showed a normal aspect of the area. Later on, the patient had multiple episodes of loss of consciousness, and in November 2004, a hypoglycaemic coma. After this episode, the patient developed a left hemispheric ischemic stroke followed by right side hemiplegia and severe mixed aphasia. Transferred to our clinic, the patient was reevaluated. Blood was sampled for glucose and insulin levels every 4-6 hours and during hypoglycaemia symptoms. The glycaemia varied between 26-54 mg/dl. The transabdominal US did not reveal a pancreatic tumour. The biochemical data showed a trend to severe hypoglycaemia when interrupting the glucose administration. During surgery the US did not show any image suggestive for insulinoma. The pancreas palpation revealed at the limit between body and tail a well delineated tumor, with a diameter of 1 cm. Immediately after enucleation, the glycaemia was 120 mg/dl. The histopathological study featured an insulinoma (Fig.1 A). After surgery the evolution was favourable. The patient was discharged surgically healed, but with severe neurological damage. One month later the patient developed a pancreatic fistula and was hospitalized. The evolution was slowly favourable, at discharge the fistula being still active (10 ml/day).

Case 3

A 75 year old female was hospitalised with refractory hypoglycaemia and neurologic symptoms. Three days before admission she suffered a sudden tonico-clonic motor crisis followed by loss of consciousness. When admitted to the neurosurgical clinic, she was diagnosed with a right, prefrontal, ischemic stroke, the CT scan showing diffuse atrophy of the cerebral cortex. The glycaemia varied between 26-40 mg/dl, the patient being permanently under i.v. administration of 10% glucose. The attempt to discontinue i.v. glucose failed as the patient showed severe confusion. Blood was sampled for glucose and insulin levels every 4-6 hours and during hypoglycaemia symptoms. C-peptide levels were $2.7 (\pm 0.2)$ ng/ml. The CT and MRI studies revealed a normal pancreas. The intraoperative US showed in the pancreas towards the pancreatic uncinate process, a tumor with transonic content. The palpation of the pancreas during surgery revealed between the lower margin of the pancreatic head and the uncinate process a nodule with a diameter of 1 cm that was surgically enucleated (Fig. 1 B-D). The histopathological examination showed an insulinoma.

The glycaemia became normal after surgery. The patient developed a pancreatic fistula in the 7th postoperative day. Under treatment, the evolution of the fistula was slowly favourable.

Discussion

The main clinical sign in pancreatic insulinoma is the impossibility to suppress the insulin endogen secretion in the presence of hypoglycaemia (5). So, due to neuroglycopenia as the direct hypoglycaemia effect, some patients can present headache, confusion, visual troubles, convulsions, personality changes, obtundation, and coma. Other patients respond to neuroglycopenia by releasing catecholamines and develop adrenergic manifestations such as palpitations, muscular weakness, shivering, tachycardia, irritability (6). Fifty per cent of the patients have both categories of symptoms (5). The biochemical diagnosis is established in 95% of the patients through the extended fasting test (up to 72 hours) when the following parameters are evidenced: the level of the serum insulin is 10mU/ml or greater, the glucose level lower than 40 mg/dl, the serum level of peptide C higher than 2.5 ng/ml (7). The imaging studies should be initiated after complete biochemical testing. Most (80%) of the benign insulinomas are smaller than 2 cm and cannot be detected by CT scan or by transabdominal US (8). The first imaging assessment is done by transabdominal US which has a sensitivity of 50%. CT sensitivity is 24% when performed with gadolinium. The contrast enhanced MRI scan has a diagnostic sensitivity of 40% (9). Scintigraphy of the somatostatin receptor has a sensitivity of 60%, although many insulinomas do not express the type 2 somatostatin receptor (10).

The endoscopic US detects about 77% of the pancreatic insulinomas. Selective angiography has 47% sensitivity (11). The intraoperative US is the most accurate method of detection for pancreatic insulinomas (90% sensitivity) (12). The size of the tumour is not correlated with hypoglycaemia severity. After insulinoma resection, the hypoglycaemia can continue for approximately 48-72 hours due to the down-regulation at the level of the insulin receptors (13).

Histological criteria to differentiate between the malignant and benign insulinomas are not available (14).

Establishing the diagnosis of the neuroendocrine tumours is difficult, even in the situation of performant investigations. An early diagnosis is almost impossible. As in our cases, all patients have neurological symptoms of different intensity due to neuroglycopenia. The imaging studies still have a decreased sensitivity and specificity.

In spite of the progress achieved, finding the pancreatic insulinomas in our cases was still based on palpatory exploration of the pancreas during surgery.

International experience has shown that in only 20% of the cases angiography is able to point out with high accuracy the location of the tumor. In our cases the angiography was inconclusive. The CT and MRI evaluation has an extremely low specificity for the localization of pancreatic insulinomas. It is speculated that the diagnosis is difficult due to the small dimensions of the tumour (15, 16).

Although there might be several nodules of insulinoma type in the pancreas, in 90% of cases only one nodule secretes insulin. The hypothesis that benign insulinomas

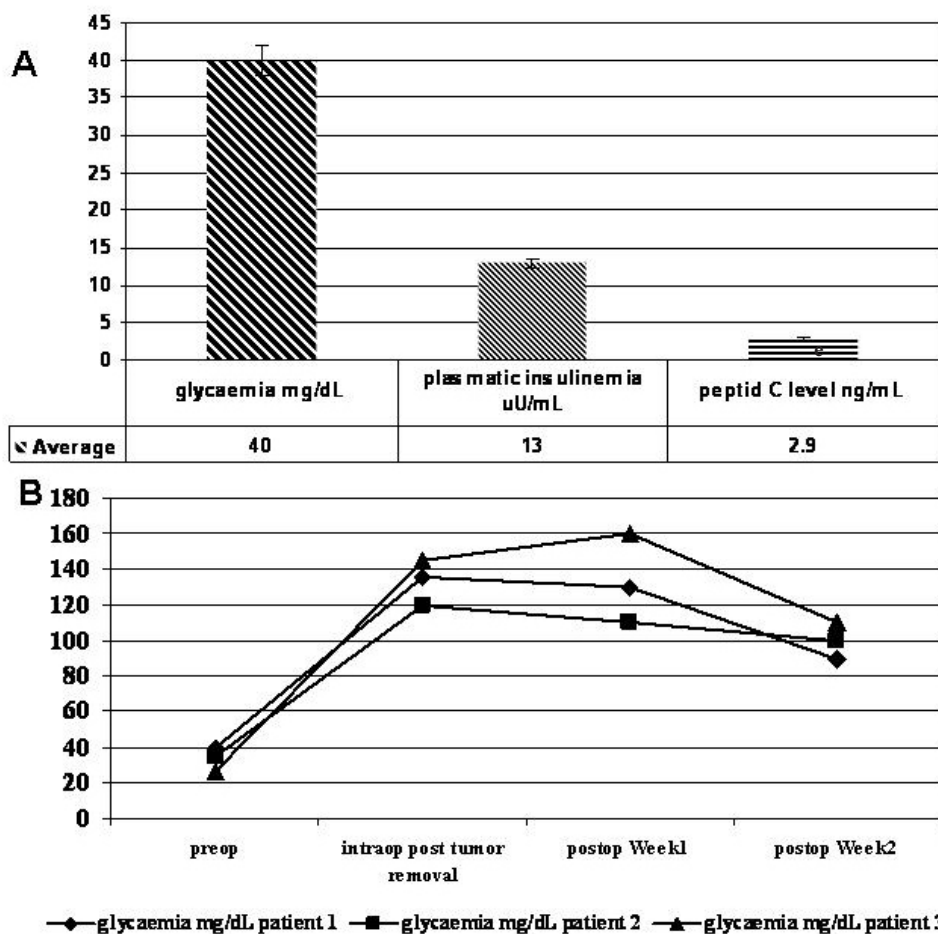


Fig.2 Serum data assessment. Glycaemia, insulinemia and plasma C peptide levels analyzed preoperatively (A). Evolution of serum glycaemia (B). Mean \pm SD.

can recur must not be ruled out. In our first case, the real problem was the recurrence of the insulinoma.

Our findings indicate that a diagnosis can be suggested by biochemical evaluation (Fig.2A), clinical symptoms (17) and by intraoperative US. Although the intraoperative US has an increased detection rate and a sensitivity of approximate 90% (18), we found that refractory hypoglycaemia combined with hyperinsulinemia are able to sustain the diagnosis. However, the intraoperative exploration of the pancreas performed by the surgeon is still cardinal.

Conclusions

Accurate preoperative detection and localization of insulinomas is essential for the appropriate selection of candidates for surgery. Future development in imaging techniques might improve the preoperative diagnosis of insulinoma.

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