Insulinoma masquerading as neurologic disease – Case report and review of the literature

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INTRODUCTION

Insulinomas are the most frequent etiology of hypoglycemia in a non-diabetic patient and the most common functional neuroendocrine tumors of the pancreas, with an annual incidence of about 4 cases per million[1, 2]. The majority of insulinomas are "well-differentiated endocrine tumors" or grade 1 tumors, as defined by World Health Organization[3]. Most tumors are benign, solitary and occur sporadically. However, about 10% are associated with multiple endocrine neoplasia type 1 (MEN-1)[1,2].

Despite the majority being benign tumors, hypoglycemic symptoms caused by the hyperinsulinemia are frequently debilitating[4]. Whipple triad (hypoglycemia, symptoms of hypoglycemia – either adrenergic or neuroglycopenic – and relief of these symptoms after administration of glucose) is usually present and should alert to the diagnosis[2,5].

After the diagnosis is made, locating the tumor can be challenging because most tumors are small[4]. Nonetheless, locating the tumor is crucial, once the only definite treatment is surgical excision[1,2]. The majority of patients reach normalization of glucose levels after surgery. Incomplete resection leads to persistent symptoms and although uncommon in sporadic insulinomas, recurrence can be as high as 20% in patients with MEN-1 syndrome[6,7].

Keywords: Insulinoma. Endocrine Tumors. Hypoglycemia.

Palabras clave: Insulinoma. Tumores endocrinos. Hipoglucemia.

CASE REPORT

A healthy 36-year-old male was admitted in the emergency room with altered mental status and hypoglycemia (50 mg/dL). The patient recalled recurrent symptoms of diaphoresis, tremors, blurred vision and palpitations, sometimes with loss of consciousness and incontinence of urinary sphincter, for the past 4 months. Blood glucose levels had never been evaluated during these episodes. Because of these symptoms, he consulted with a Neurologist and was diagnosed with epilepsy and started on levetiracetam 500 mg twice daily. Cranial tomography and cranial magnetic resonance were unremarkable.

A careful anamnesis allowed to better clarify these symptoms: they occurred before meals and were relieved with eating carbon hydrates; they were associated with weight gain and there had been no improvement with the use of the anticonvulsive therapy. He had no family history of endocrine disease. Physical examination was unremarkable.

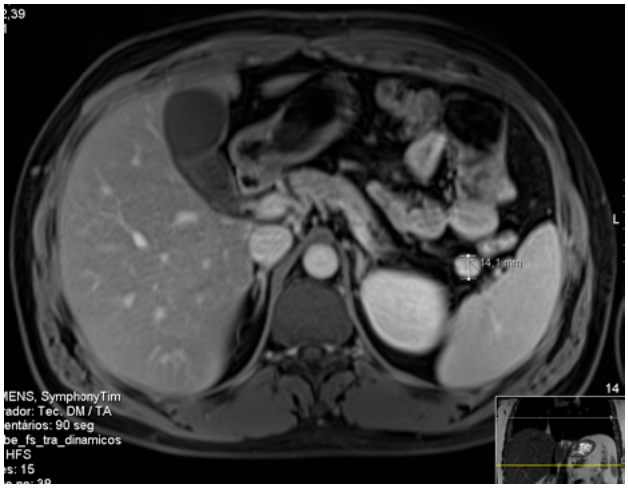
A prolonged supervised fasting test was applied and led to symptomatic hypoglycemia with hyperinsulinemia (Table 1).

Anti-insulin antibodies were negative. Other hormonal studies, including serum morning cortisol, parathormone (PTH) and adrenocorticotropine (ACTH) levels were normal, making the diagnosis of multiple endocrine neoplasia unlikely.

Abdominal magnetic resonance (MRI) demonstrated a well-defined enhanced lesion in the tail of the pancreas measuring 14mm (Image 1).

Because of its location near the spleen, questioning whether the lesion was intrapancreatic or an accessory spleen, a ^{68}Ga-DOTA-NOC PET scan was performed. On the PET scan, there was a discrete expression of somatostatin receptors adjacent to the lateral end of the tail of the pancreas, in the same location as in the MRI (Image 2).

Image 1. Abdominal Magnetic Resonance – there is a well-defined enhanced lesion in the tail of the pancreas.



He maintained severe hypoglycemia despite glucose fluid administration and nutritional adequate plan so he was started on medical therapy with octreotide 300 mg daily and diazoxide 900 mg daily.

Table 1

	6h	7h	8h	10'	20'	30´
Glucose (mg/dL)	55	40	38	54	75	88
Insulin (uUI/mL)	60,1	52,1	68,7	24,1	28,8	194,7
C-Peptide (ng/mL)	6,25	5,96	7,07	4,4	4,09	10,8

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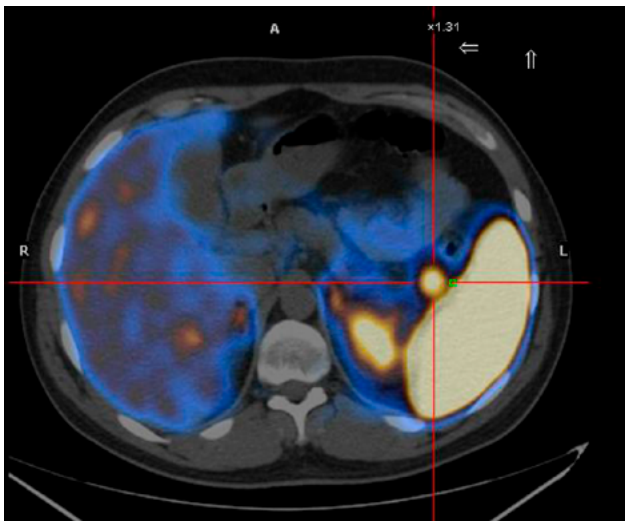
Image 2. 68Ga-DOTA-NOC PET-SCAN - Discrete expression of somatostatin receptors adjacent to the lateral end of the tail of the pancreas.



Nodule enucleation was performed by laparoscopy surgery, with no immediate complications. Pathological examination revealed an encapsulated pancreatic mass measuring 17x14x15mm. Mitotic index was <2 per 10 consecutive high-power fields (HPF) and proliferation index ki-67 was estimated <2%, making the diagnosis of low grade neuroendocrine tumor of the pancreas. Tumor cells showed a positive staining for insulin, synaptophysin and cromogranine in the immunohistochemical analysis.

Shortly after surgical treatment, glucose levels increased to the normal range.

The patient was discharged without any hypoglycemic symptoms after 7 days. He remains asymptomatic 6 months after surgery.

DISCUSSION

The symptoms of insulinoma are usually nonspecific and can vary. Hypoglycemia can present either with adrenergic symptoms, such as palpitations, tremor, anxiety, hunger or sweating, or neuroglycopenic symptoms, such as slurred speech, mental confusion, blurred vision, difficulty to concentrate or epilepsy episodes[1,2,6,8]. These symptoms may be attributed to either psychiatric or neurologic diseases, delaying the diagnosis[1]. Measuring blood glucose levels upon these symptoms is therefore crucial to adequate diagnose a hypoglycemia.

The diagnosis of an insulinoma should be thought when a previous healthy non-diabetic individual presents with hypoglycemia[9]. Hypoglycemia usually occurs after a fasting period or is triggered by exercise, but postprandial hypoglycemia may also occur and does not exclude the diagnosis[1,10].

After a symptomatic hypoglycemia with hyperinsulinemia is documented, the diagnosis of insulinoma is made. This occurs more often following a 72h prolonged fasting test, which is the gold standard for diagnosing an insulinoma[4]. The biochemical pattern of insulinoma is hypoglycemia (blood glucose levels < 55mg/dL) with inappropriate insulin and C peptide levels (> 3uU/mL and >0,2 nmol/L, respectively)[4,11]. Once insulinoma is diagnosed, genetic testing for MEN1 is recommended[2].

Following diagnosis, localization is essential once the definite curative treatment is surgery[1,2]. Insulinomas are typically small nodules; the majority is smaller than 20 mm, making its localization challenging[4,7]. As insulinomas are almost always found in the pancreas, image techniques should be directed at the upper abdomen[4]. Contrast enhanced computer tomography (CT) scan, magnetic resonance imaging (MRI) and trans abdominal ultrasonography may locate approximately 75% of insulinomas[11]. CT scan is usually the first to consider as it has a sensitivity greater than 90% in detecting insulinomas[4].

When anatomic localization is either negative or unclear, more invasive techniques such as endoscopic ultrasound (EUS) or selective intra-arterial calcium stimulation with hepatic samples may be necessary[4,11,12]. Nuclear imaging is based on the expression of certain receptors in neuroendocrine tumors. Because a large variety of endocrine tumors express somatostatin receptors[4], imaging with somatostatin analogs may help to locate the tumor and also inform about the potential use of radionuclide therapy in metastatic tumors[13]. Positron emission tomography (PET) with radiotracers such as 18F-fluorodeoxyglucose (18F-FDG) or 18 F- dihydroxyphenylalanine (18F-DOPA) can also be used in the detection of insulinomas[4]. The first is of limited use because most insulinomas have low FDG uptake[14]. When even with all these available modalities the location of the insulinoma is not apparent pre-operatively, intraoperative pancreatic ultrasonography almost invariably localizes the tumor[7,11].

Surgery is the treatment of choice is curative in the majority of the cases[1,7]. Surgical procedure depends on the size and the location of the tumor[6,15] with laparoscopic surgery being the most used currently[7]. Surgical techniques include tumor enucleation or pancreatic resection[1]. If the tumor is small and solitary, tumor enucleation is the procedure of choice[4,15]. Pancreatic resection (distal or median pancreatectomy or pancreaticoduodenectomy) is reserved for adherent lesions, tumors too close to adjacent structures or if malignancy is suspected[1,15].

Histologically, insulinomas show diffuse expression of neuroendocrine markers, such as synaptophysin and chromogranin[8,12]. Well-differentiated tumors may be distinguished from poor-differentiated ones by mitotic rate (number of mitose per 10 HPF) and proliferation index (Ki-67 proliferation index). Histologically, there are no markers of malignancy, and the diagnosis is made once metastasis occurs[12].

Medical treatment of insulinomas is aimed at preventing hypoglycemia and is generally used prior to surgery, in unresectable tumors or inoperable patients, or when patients refuse surgery[1,7,11,12]. Diet, including frequent feedings with long acting carbon hydrates, diazoxide or octreotide may

be tried even though restoring euglycaemia with the use of pharmacological drugs is difficult[1,7,8].

In poor surgical candidates, alcohol ablation, radiofrequency ablation and embolization of the tumor are other possible therapeutic options[4,7].

CONCLUSION

Insulinomas are rare neuroendocrine tumors, the majority is benign and sporadic, but it can be part of the MEN-1 syndrome[1]. The diagnosis of insulinoma may be challenging due to its rarity and variable presentation. O other diseases, such as neurologic, may be considered first[1,7]. It is important to considerer the diagnosis since chronic and severe hypoglycemia can be fatal.

Biochemical diagnosis is usually easy, but preoperative localization may be demanding. CT scan may be used as first line, with other imaging techniques being reserved for tumors undetected on CT[4,7].

Surgery is the treatment of choice and is usually curative. Restoring euglycemia prior to the may be difficult and multiple drugs are usually needed[1,7].

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