

# Where's the Insulinoma? A clinical case report

Raquel Cavaco\*, Márcia Man\*\*, Alda Jordão\*, J. Raposo\*\*\*, J. Gorrão Clara\*

### Abstract

The suspicion of an insulinoma in an individual with adrenergic symptoms and / or neuroglycopenia must be the first concern in the differential diagnosis of hypoglycaemia. Insulinoma is the most frequent endocrine tumor of the pancreas and appears at any age, being more frequent between 40 and 60 years. The diagnosis is clinical and can be difficult to make in the presence of doubtful symptoms of neuroglycopenia or adrenergic symptoms after meals. Whipple's triad of - glycemia below 50 mg/dl and symptoms / signs of hypoglycaemia that revert with administration of glucose - is strongly suggestive of insulinoma, and when associated with blood insulin inadequately high, the diagnosis is of insulinoma. The authors describe the case of a 58-year-old male patient, with a clinical picture characterized by multiple episodes of confusion, migraine, bewilderment, irritability, agitation and diaphoresis, progressing for almost 8 months. The complaints were not properly

evaluated initially and the patient was treated with sedative drugs. A fasting glycemia of 38 mg/dl made insulinoma a probable diagnosis and this was confirmed by the 72 hour fasting test. Difficulties arose, as usual, in locating the tumor with imaging methods (abdominal-pelvic ultrasound and computerized tomography scan, octreotide scan and endoscopic ultrasound) and only selective arteriography with catheterization of the branches of the celiac artery revealed the tumor, located in the head of the pancreas. Surgical treatment consisted of tumor enucleation. The histological findings confirmed the diagnosis of benign insulinoma. The peculiarities of the diagnosis and particularities of the image studies in insulinoma are discussed in this article.

Key words: insulinoma, hypoglycaemia, hyperinsulinemia, neuroglycopenia symptoms, 72 – hours fasting test, arteriography, enucleation.

### Introduction

Insulinoma is a rare neuroendocrine tumor, made up mainly by pancreatic  $\beta$ -cells producing an excessive amount of insulin. It is the most frequent endocrine tumor in the pancreas – an incidence of 1/1,000,000 inhabitants – and in around 80% of the cases it is a one only benign occurrence. The ratio male / female gender is 2:3, being 50 years the average age at the time of diagnosis. The insulinoma diagnosis is typically late, it can happen from a few months to several years after the symptoms onset. Whipple's triad – anecdotal hypoglycemia, central nervous system dysfunction, related with hypoglycemia and reversion of neuroglycopenia regression after taking glucose – it strongly suggests insulinoma.

Clinical diagnosis can be difficult to reach, reason why, when necessary it must be made the prolonged fasting test, which, if positive, confirms the hypothetical diagnosis. The key to the biochemical test relies on showing hypoglycemia while in the presence of inadequately high levels of serial insulin.

The pré-surgical investigation to locate the tumor may include a multitude of imagiology tests, from ultrasound scan to angiography.

### Clinical case

58-year-old male patient, Caucasian, machinery technician, with hypertensive antecedents, diagnosed 5 years ago and under medication with ACE inhibitors, chronic gastritis and sinus pathology. Without alcohol or smoking history nor other drug intake apart of those mentioned, particularly, sulfonyleurea intake.

The patient has been followed in the Otolaryngology service for 3 years, due to sinus pathology and an elective surgery to correct the nasal septum is scheduled; asymptomatic, spontaneous hypoglycemia in fasting, was detected while in pre-operative preparation tests. For this reason he was referred to an Internal Medicine service having at that point in time, being found 4 episodes characterized by its association with neuroglycopenia symptoms – gene-

\*Hospital Pulido Valente Internal Medicine II Service

\*\*Pneumology, Hospital Pulido Valente

\*\*\*Hospital Pulido Valente General Surgery Service

Received for publication on the 11 January 07

Accepted for publication on the 18 March 08

TABLE I

## Prolonged Fasting Test results

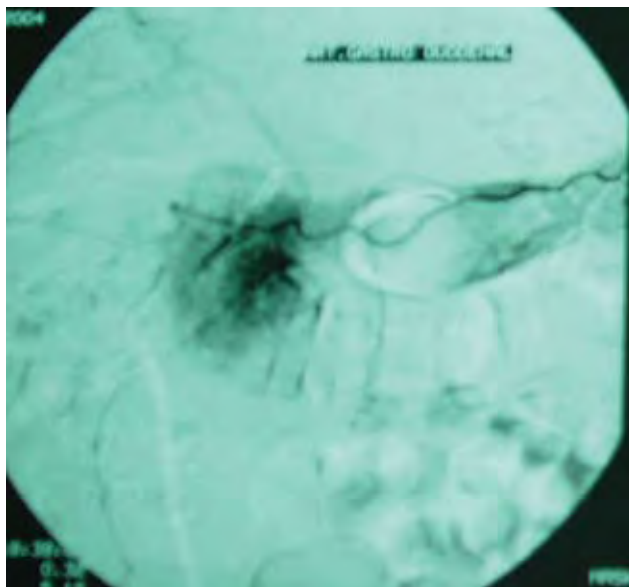
Prolonged Fasting test	12 hours fast	15 hours fast	18 hours fast
Glycemia	55 mg/dL	27 mg/dL	24 mg/dL
Insulinemia	14,9 mU/L	15,6 mU/L	20,1 mU/L
Serial C peptide	3,5 ng/mL	4,5 ng/dL	4,6 ng/dL

Prolonged Fast results (Reference range: glycemia 70 – 110 mg/dL; insulinemia 6 – 27 mU/L; serial C peptide 0,9 – 4 ng/dl). The test started at 9PM in the previous day and ended at 6 PM due to neuroglycopenia symptoms onset.

ralized headache, lethargy – and adrenergic symptoms – tremor, hyperhidrosis, mental confusion and anomalous behavior (psychotic type). These episodes had occurred in the last eight months, with 1 to 2 months interval, starting before the main meals and would ease as food was taken. When questioned directly, he confirmed he would have more meals than his work mates, around 7/day. The patient had already been seen, at his health centre for such complaints having been prescribed anxiolytic therapy.

On the physical exam he showed to be alert, communicating and cooperating, oriented in time and space as well as auto and allopsychic orientation, pink and hydrated skin and mucosa, anicteric sclerotic, android obesity, arterial pressure 140/82 mmHg and heart rate 100 bpm. Cardio-pulmonary auscultation and abdominal palpation showed no alterations. A short neurological exam showed no alterations either.

As this was a patient with repeated episodes of asymptomatic fasting hypoglycemia and, simultaneously, postprandial hypoglycemia with adrenergic symptoms and neuroglycopenia, we chose a prolonged fasting test, to confirm the hypothetical diagnosis of insulinoma. This was positive, having been suspended at 6PM due to the onset of neuroglycopenia symptoms – somnolence followed by psychomotor restlessness, and behavioral changes featured by marked aggression and verbal abuse – while inadequate serial hypoglycemia and hyperinsulinemia were present (Table I). 6 formula of IV hypertonic glucose were administered with a subsequent clinical improvement. From the remaining laboratory tests performed, it is of notice: thyroid function, total calcium and prolactin



Selective arteriography image: “we can see a nodular image at the head of pancreas level, about 1,5 cm (3/5 inches) diameter, hypervascular, with a late blush, supplied by the superior gastroduodenal and mesenteric arteries”.

FIG. 1

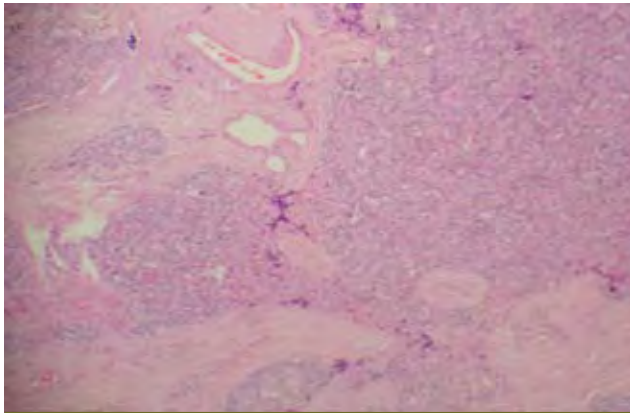
within the reference range. Having established the biochemical diagnosis of insulinoma, it was attempted to locate the tumor pré-operatively.

Among all Imagiology methods used, are to highlight: abdominal ultrasound – (...) without significant changes; abdominal-pelvic CT Scan with contrast – (...) pancreas with homogenous dimensions and densities, without nodular images, nor abnormal contrast capture (...); ocreotide scan – (...) it did not show any lesion suggesting an insulinoma; endoscopic ultrasound – (...) there were no images of suspected lesions taking space; and a selective arteriography with the celiac artery branches catheterized – (...) has revealed a nodular lesion, with around 1,5 cm, the head of pancreas, supplied by the superior gastroduodenal and mesenteric arteries (Fig. 1).

The patient was transferred to the Surgery Service, having undergone surgery with tumor enucleation. It should be mentioned that intra-operatively there were no macroscopic signs of secondary lesions.

Histological findings confirm to be a neuroendocrine neoplasm compatible with a clinical diagnosis of insulinoma (Fig. 2).

The patient was discharged and referred to Me-



**Histology Aspects.** Report made by Hospital Pulido Valent Anatomical Pathology Service. "We can see, in a wide amplification, the tumoral architecture, featured by a lobule pattern. The lobules are separated by fibrous stroma, rich in vessels and made of relatively monomorphic cells with moderated pleomorphism and clear round nuclei with granular chromatin (neuroendocrine nuclei features)".

**FIG. 2**

dicine and General Surgery appointments. He was evaluated at the Medicine appointment every quarter and around 1 year later, he has *again* no hypoglycemia or iatrogenic diabetes.

### Discussion and conclusions

In most cases, the clinical frame is so typical that enables the diagnosis of insulinoma just on clinical criteria;<sup>1,2,3</sup> however, there are other cases where a clinical approach on its own leaves us in doubt and before such situations it is imperative to do the prolonged fasting test, in order to show Whipple's clinic triad,<sup>3,4</sup> in association with inadequate increase on serial hypoglycemia and C peptide (the increase on C peptide confirms the endogenous origin of insulin).<sup>5, 6,7</sup>

The imagiology study, to locate the tumor, must start only after being reached the biochemical diagnosis, as 80% of insulinoma are less than 2cm wide in diameter and might not be visible both in the ultrasound or tomography. Even after confirming the biochemical diagnosis the success of pre-operative location happens in less than 60% of the cases,<sup>2,8</sup> reason why there is a growing consensus that pre-operative location techniques have a relative usefulness and they will be, gradually replaced by intrasurgical ul-

trasound and intraoperative palpation of the lesion by an experienced surgeon.<sup>2,3</sup>

Despite not having exclusive histological or immunohistochemical criteria, in the current literature, enabling to anticipate an insulinoma biologic and clinical behavior, the histological aspects seen in this case (less than 2 cm, less than 2 mitosis/ 10 high resolution field, proliferation score – Ki67- less than 2%, no necrosis and no metastases), favor a macroadenoma diagnosis. According to the publication *Tumor of endocrine organs WHO*,<sup>9</sup> malignant tumors are bigger and in around 1/3 of the cases do show hepatic metastases at the time of diagnosis.

The first line of therapy in apparent benign cases is the tumor enucleation, once the cure is achieved in 90% of the cases. The therapy options in malignant tumors, obviously depend, on the staging, implying in most cases, wider recession and eventually chemotherapy. The medical therapy (diazoxide, somatostatin) is advocated only in malignant tumors, in non-located benign tumors or those without a surgical indication.<sup>10</sup> ■

### References

1. Karam JH, Masharani U. Hypoglycemic Disorders. Capitulo 18. Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. Harrison's - Principles of Internal Medicine 16th Edition. USA. Mc Graw Hill 2005: 747-765.
2. Endocrinology. Pancreatic & Duodenal Neuroendocrine tumours. Capitulo 26. CMTD 2004. :1131-1132.
3. Diabetes Mellitus & Hypoglycaemia. Hypoglycemia duo to Pancreatic B Cell Tumours. Capitulo 27. CMTD 2004:1186-1188.
4. Endocrinology. Multiple Endocrine Neoplasia. Capitulo 26. CMTD 2004: 1142-1143.
5. Sapountzi P, Charnogursky G, Emanuele MA, Murphy D, Nabhan F, Emanuele NV. Case Study: Diagnosis of Insulinoma Using Continuous Glucose Monitoring System in a Patient with Diabetes. Clinical Diabetes 2005; 23: 140-143.
6. Yamaguchi M et al. A case of insulinoma with frequent hypoglycaemic attacks not showing evident hyperinsulinemia. Nippon Naibunpi Gakkai Zasshi 1992; 68: 1269-1275.
7. Chammas NK, Teale JD, Quin JD. Insulinoma: How reliable is the biochemical evidence? Ann Clin Biochem 2003; 40: 689-693.
8. Tsagarakis S et al. Regionalization of occult pancreatic insulinomas with the arterial stimulation venous sampling (ASVS) technique. Clinical Endocrinology 1997; 47: 753-757.
9. Komminoth P, Rindi G, Perren A, Heitz PhU, Oberg K, Kloppel G. Insulinoma. Tumours of Endocrine Organs WHO 2004: 183-186.
10. Oberg K et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumours of gastroenteropancreatic system. Annals of Oncology 2004; 15: 966-973.