INSULINOMA – CASE REPORT

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Abstract: *Insulinoma is an insulin secreting tumour, developed from pancreatic ß islet cells, characterized by the independent hypersecretion of insulin. 80% of these tumours are unique and benign, and about 10% of cases are malignant, the remaining being multiple benign tumours (50% of which are associated with multiple endocrine neoplasia syndromes). The diagnosis is suspected in a patient with symptomatic hypoglycemia, clinical manifestations constituting the "Whipple triad". We report the case of a patient aged 70 from Sibiu, known with stage II hypertension risk group C, and stage II obesity, showing association of the insulinoma with a tumour of the left adrenal gland (hyperplasia of the fascicular area). Genetic screening for the identification of a MEN syndrome was not performed.*

INTRODUCTION

Insulinoma is an insulin secreting tumor developed from pancreatic ß islet cells, characterized by increased insulin secretion, independent from the glucose self-regulating system. The incidence of the disease is approximately one case per 250,000 patients/year, occurring in a proportion of 60% in women, the average diagnosis age being 50 years.(1) 80% of these tumours are unique and benign, in about 10% of the cases they are malignant, and the rest are multiple benign tumours.(2) In 99% of the cases the tumour belongs to the pancreatic tissue, having small dimensions (between 1 and 50 mm). 50% of the multiple tumours are associated either to multiple endocrine neoplasia syndrome: MEN1, Von Hippel - Lindau syndrome, or to pheochromocytomas, usually diagnosed around the age of 20.(3)

The patients with insulinoma exhibit symptomatic hypoglycemia due to neuroglycopenia (anxiety, dizziness, unusual behavior, confusion, blurred vision, leading to convulsions and even hypoglycemic coma) and catecholamine release (palpitations, sweating, tachycardia, tremor, increase of blood pressure, paleness).(1,4)

The diagnosis is suspected in a patient with symptomatic hypoglycemia, the clinical manifestations constituting the "Whipple Triad", a certification element for the diagnosis of insulinoma: signs and symptoms of hypoglycemia, plasma glucose level ≤ 45 mg / dl at the time when symptoms are present, the reversibility of symptoms after glucose administration.(2)

A positive diagnosis is based on the presence of inappropriately elevated levels of insulin in the face of hypoglycemia, an fasting insulin / glucose ratio > 0.33, Peptide C determination or oral glucose tolerance test over a period of 5 hours.(1,5) Suppression tests may also be used (prolonged fasting over a period of 72-hour, hospital overnight surveillance; peptide C suppression test), or stimulation tests (glucagon or i.v. calcium test).(1,2) To locate the tumour, either non-invasive (CT, MRI, nuclear imaging), or invasive imaging methods (endoscopic ultrasound, angiography, intraoperative pancreatic ultrasound) are being used.(6,7,8)

The treatment of choice is represented by the surgical removal of the tumour, this being curative in most cases.(9) When tumours cannot be located, blind resection is required, with an increased rate of complications (between 31.5 - 55%).(4) Postoperative evolution is usually favourable, with the complete remission of symptoms; in about 10% of the cases the onset of secondary diabetes mellitus is recorded.

In case of surgery contraindications, one can try medication as a treatment. The first line of therapy is with prolonged action Somatostatin analogs (Octreotide, Lanreotide).(9,10) Everolimus, a selective inhibitor of mTOR (mammalian target of rapamycin) and Sunitinib (oral inhibitor of VEGFR) have recently been approved for the treatment of advanced forms.(7,10)

I am presenting the case of a patient with insulinoma associated with a tumour of the left adrenal gland, stage II hypertension and stage II obesity.

CASE PRESENTATION

I report the case of a 70 year-old patient from Sibiu, I. P., known with stage II hypertension, risk group C, who neglected therapy at home, and stage II obesity. The family history records are without pathological meaning, no alcohol consumption, nonsmoker.

The patient was admitted for investigations in the Diabetes and Nutrition Department Sibiu, with frequent episodes of dizziness, obnubilation, states of psychomotor agitation, reaching even unconsciousness, attention and memory disturbance, speech impairment, heartburn, hunger sensation, low glycemic values (48 mg%) recorded randomly at home with the glucose meter of a person who had diabetes. The blood sugar level was recorded postprandial, after a low dietary intake.

From the patient's history we have recorded that the onset of the symptoms was insidious, about a year ago. The patient had been complaining of dizziness, fatigue, effort and „à jeun" faintness, heavy sweating, balance disorder, with remission of symptoms after hyperglucidic intake. For several

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times she was directed to the Neurology Clinic and the hospital for Neuro-Psychiatry by her family doctor, on the foreground of neuro – psychological symptoms, the patient refusing to undertake these exams. She displayed significant weight gain, of about 6-7 kg in the last year. She had never received a glycaemia test or an "à jeun" blood glucose test.

Current symptoms were first observed one month ago. Upon admission the patient was confused, time-space disoriented, quite non-cooperative with pale and wet skin, well - represented subcutaneous tissue, with predominance of abdominal obesity - BMI = 33 kg /sqm. Blood pressure at admission was 200/100 mm Hg, heart rate of 96 / min, rhythmic. During hospitalization the patient displayed, especially in the morning or on an inadequate dietary intake, episodes of psychomotor agitation, associated with cold sweat, hunger sensation and obnubilation.

Laboratory investigations at the time of admission revealed that „à jeun" venous blood glucose was 42 mg%; the rest of the clinical and paraclinical investigations showed no pathological changes.

On the 3rd day of hospitalization the fasting values of insulin = 52 μU / ml (normal values 10-20 μU / ml) and glycaemia = 37 mg% were measured. The fasting insulin / glucose ratio (μU / mL) / (mg/dl) report was 1.40 (in insulinoma the ratio is> 0.33). Dosage of Proinsulin, C - peptide, anti-insulin antibodies could not be performed. On the first day of hospitalization we determined the glycemic profile, followed by random glycaemia measurements with a glucose meter when symptoms were present (Table no 1).

Table no. 1. Blood glucose values recorded during hospitalization

Time of Glucose Test / **Glucose value (mg/dl)**	7^{00}	12^{30}	15^{30}	18^{30}	21^{30}	24^{00}	03^{00}
Day 1	63	34	118	71	53	47	61
Day 2	39	-	-	-	-	-	-
Day 3	37	54	-	287*	-	76	-
Day 4	-	-	30	363*	55	-	-

*Glucose values were measured after intravenous 10% and 33% glucose administration.

The glycemic profile values from the first day of hospitalization showed a flat curve, the maximum values reached only 118 mg/dl (at 15^{30}). Repeated fasting and daytime blood glucose dosing showed values below 50 mg%.

It was not considered appropriate to perform an oral glucose tolerance test or 72 hours prolonged fasting because clinical and paraclinical data already directed the diagnosis towards suspicion of insulinoma, and neuroglycopenia symptoms were severe, causing the patient to refuse the tests. Neurological examination and EEG excluded other causes for the loss of consciousness. Abdominal imaging revealed a 12 mm tumour at the level of the pancreatic tail and another one of 30/25 mm in the left adrenal gland (CT conclusions: pancreatic tail tumour - possibly insulinoma, left adrenal gland tumour) (table no. 2).

Table no. 2. Abdominal imaging results

Abdominal ultrasound	**Barium swallow test**	**Abdominal CT**
did not provide conclusive data (meteorized abdomen, shielded pancreas, patient's non-compliance with the examination)	did not reveal gastric hyperkinesia (a determinant cause of hypoglycemia), nor the presence of other gastrointestinal changes (ulcerative disease, gastrointestinal anastomoses etc.)	made with contrast substance - highlights a small size pancreas, showing at the tail an intens iodophilic tumor, of approximately 12 mm in diameter; also the left adrenal gland presents a solid moderate iodophilic tumour, of 30/25 mm in size. No local or metastatic infiltrative lesions have been identified.

The diagnosis of insulinoma was based on:

1. patient's anamnesis and clinical manifestations (she presented the Whipple triad);
2. paraclinical tests: elevated levels of serum insulin correlated with high fasting insulin / glucose ratio (1.40) in the presence of hypoglycemia; suggestive abdominal imaging.

Treatment:

The treatment was symptomatic, aiming preoperative and surgery preparation:

1. General: in our clinic the patient received a low sodium diet, with 6 meals / day, and if she presented symptomatic hypoglycemia or glycemic values below 65 mg/dl, parenterally glucose solutions of 10% and / or 33% concentration were administered;
2. Hypotensive treatment consisted of angiotensin converting enzyme inhibitors and diuretics, maintaining blood pressure values around 145/80 mmHg.
3. Surgical: 2 weeks after discharge from our hospital, caudal splenopancreatectomy was performed in a surgery clinic in Bucharest.

The postoperative evolution, based on the discharge papers obtained by the patient from the surgery clinic, was favourable, with surgical healing. The anatomopathological examination result showed the existence of a non-malignant insulinoma, located in the pancreatic tail, associated with an adenomatous hyperplasia of the left adrenocortical fascicular area with no malignancy characteristics. The remaining pancreatic tissue mass was approximately 30%.

About one month after discharge from the Bucharest surgery clinic, the patient returned for glycemic monitoring to Sibiu County Hospital - the Diabetes Department. The overall condition was clearly improved, there were no episodes of hypoglycemia in the meantime, but secondary diabetes mellitus was diagnosed. The patient had moderately elevated glycemic values (fasting glucose was 136 mg / dl and 2 hours postprandial was 248 mg/dl), well controlled by the hypoglucidic diet instituted. Oral glucose tolerance test has not been done.

The disease outcome was good, due to complete surgical resolution, with improvement of the general condition, disappearance of hypoglycemic episodes, but with the installation of secondary diabetes, currently treated by diet. In the absence of specific treatment, the outcome would have been reserved, with a progressive deterioration of the general and neurological condition (repetitive post-hypoglycemic encephalopathy), with the danger of traumatic fallouts, resulting in marked deterioration in quality of life.

Case specifics:

The presence of an insulinoma associated with a left adrenal gland tumour, whose potential involvement in limiting hypoglycemia through secretion of glucocorticoid hormones could not be demonstrated, due to the impossibility of their dosage.

There was no evidence of a clear etiopathogenic link between the elevated pre-operative blood pressure and the adrenal tumour, since moderately elevated blood pressure values maintained after surgery, even under hypotensive medication; it is probably essential high blood pressure, aggravated by hypoglycemia.

The onset of secondary diabetes after surgery, well controlled with a 160 carbohydrate diet.

DISCUSSIONS

Although psycho - neurological symptomatology prevailed, the disappearance of symptoms after glucose intake did not direct ambulatory investigations towards hypoglycemia.

Routine abdominal imaging (abdominal ultrasound, barium swallow test) did not reveal the presence of the tumours, which demonstrates their limited effectiveness in locating gastrointestinal neuroendocrine tumours.

Although the abdominal CT showed the concomitant presence of a tumour in the left adrenal gland, for financial reasons, no further investigations were completed to exclude or confirm hormonal secretion at this level.

Although the literature data shows the onset of secondary diabetes in only 10% of cases, our patient presents diabetes mellitus, currently controlled by diet.

Although the patient has insulinoma associated with a left adrenal gland tumour (hyperplasia of the fascicular area), genetic screening to identify a MEN syndrome has not been performed.

CONCLUSIONS

This case supports the importance of detailed anamnesis, which speeds up the diagnosis, before the occurrence of irreversible complications.

Advances in pre- and intraoperative diagnosis (CT, IMRI, intraoperative pancreatic ultrasound) allow the localization and complete resection of insulinoma.

For the treatment of insulinoma, early surgical intervention is recommended in order to prevent hypoglycemic encephalopathy sequelae, regardless the risk of secondary diabetes onset.

Completing investigations for the diagnosis of a multiple endocrine neoplasia syndrome is important for both further monitoring of the patient and for prophylactic care of progeny.

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