

# Insulinoma – diagnosis and treatment based on case description

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## Abstract

A 56-year-old patient was admitted to the Department due to recurrence of symptoms: sudden weakness, dizziness, excessive sweating, palpitations, which cleared up after food intake. Physical examinations and initial diagnostic tests did not reveal any abnormalities. Abdominal ultrasonography and magnetic resonance showed a heterogenous tumour of the pancreas with features of insulinoma. The prolonged supervised fast test that was applied induced hypoglycaemic symptoms. The level of glucose and insulin was at the lower range of the fast test. The tumor was surgically removed, and the suspicion of insulinoma was confirmed by histopathologic examination.

## Key words

insulinoma, pancreatic tumours, hypoglycemia

## INTRODUCTION

Pancreatic neuroendocrine tumours (PET) are relatively rare. The majority of such tumours are benign and constitute less than 5% of all primary pancreatic malignancies. There are 2 main groups of PETs: functional PETs that secrete hormones and cause hormone-dependent symptoms, and non-functioning PETs without hormonal secretion. Functional PETs include: insulinoma, glucagonoma, somatostatinoma and gastrinoma. The most common of these is insulinoma which derives from the beta cells of pancreatic islets producing insulin and cause hypoglycaemia. The present paper describes the case of a patient who developed symptoms of Insulinoma [1, 2].

## CASE REPORT

A 56-years-old patient with no history of chronic diseases was admitted to the Department of Internal Medicine because of recurrent onsets of sudden weakness, dizziness, excessive sweating, palpitations, which were relieved after food intake. The patient had experienced the symptoms for approximately 2 years, especially at midday and after exertion, occasionally at night. She denied experiencing loss of consciousness, dyspnea, chest pain, weight loss and other symptoms. Her past medical history covered a total hysterectomy and bilateral salpingoophorectomy due to uterine myomas and ovary cysts. Her family history was not significant.

On admission to the Department of Internal Medicine the physical examination was unremarkable. It revealed normal arterial blood pressure – 120/75 mmHg, not palpable lymph nodes, vesicular sound and percussion over the lungs, slightly increased, regular heart rate – 104/min. Palpation of the abdominal cavity and neurological examination did not reveal any pathologies. ECG on admission demonstrated regular sinus rhythm of 100/min.

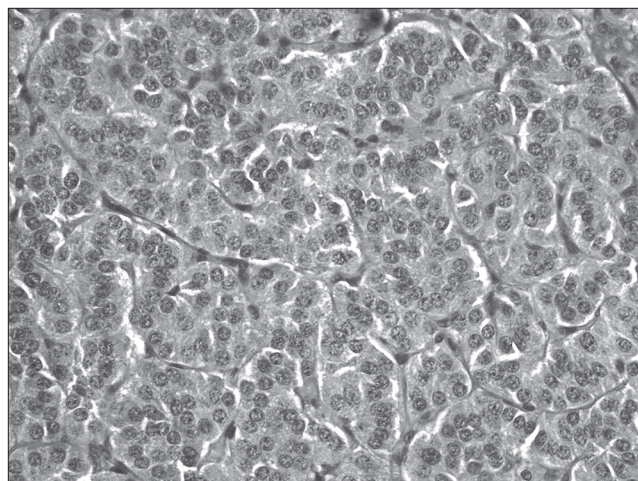
Laboratory tests performed on admission demonstrated no changes in blood morphology and urine analyses, normal values of C-reactive protein (CRP), electrolytes (Na, K, Ca), urea, creatinine, transaminases, and bilirubin. Glucose level was within normal range (97.4 mg/dl). During hospitalization, further examinations were carried out, including laboratory and radiological tests – the levels of TSH, prolactin and cortisol were within normal ranges, echocardiography, Holter ECG and a chest X-ray showed no pathologic changes.

Since abdominal ultrasonography revealed a heterogenous tumour on the border between the corpus and head of the pancreas, further examinations were planned. Control magnetic resonance (MRI) of the abdominal cavity showed a well-vascularised tumour of diameter 12 × 8 mm, with features of insulinoma localized in the same place, but no pathological changes in other abdominal organs or enlarged lymph nodes. Taking into account the typical symptoms, results of USG and MRI of the abdominal cavity, a prolonged supervised fast test was applied. Hypoglycemic symptoms occurred 20 hours after the start of the test, and blood samples taken immediately afterwards showed a glucose level of 41 mg/dl, plasma insulin 6.12 µIU/ml and insulin/glucose ratio 0.14 – values at the lower range for the fast test, which suggested the possibility of hormonal activity of insulinoma.

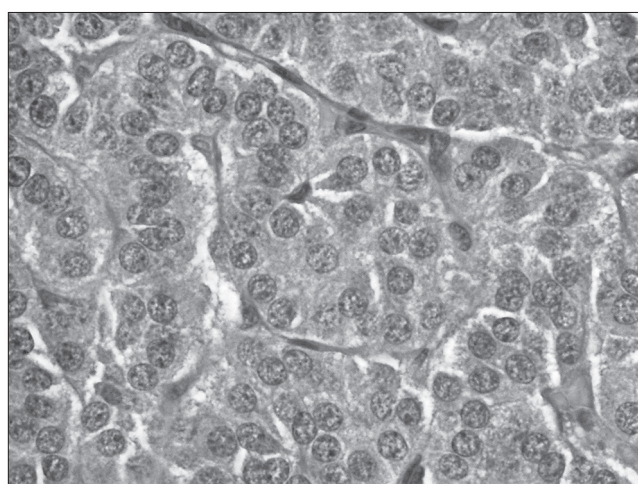
The patient underwent a surgical operation for removal of the pancreatic tumor, and subsequent histopathologic exa-

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**Figure 1.** Histopathology of endocrine tumour of pancreas (H+E Magn. 100x)



**Figure 2.** Histopathology of endocrine tumour of pancreas (H+E Magn. 400x)

mination revealed a neuroendocrine tumour NET G1 with positive staining for insulin (Fig. 1, Fig. 2). The patient did not complain of any symptoms and the glucose and insulin levels were normal at the postoperative period.

## DISCUSSION

The incidence of neuroendocrine tumours is relatively low (4 new cases per million persons a year). The most common of these is insulinoma which constitutes 70% of functional neuroendocrine pancreatic tumours. It is a tumour which derives from the beta cells of the pancreatic islet secreting insulin and thus capable of causing hyperinsulinemia as well as hypoglycaemia. In 90% of these cases it is a single, benign and encysted tumour with high vascularisation. Some 66-80% of them are not more than 2 cm in diameter. The tumour can also constitute a part of the MEN1 syndrome where it exhibits multiple incidence. Around 8-10% of insulinomas are malignant with local invasions and para-aortic lymph node and liver metastases. The tumour typically locates itself within the head as well as the body of the pancreas. However, 2% of ectopic insulinomas can be observed located in the stomach wall, intestine or frill. Apart from insulin, it can also secrete gastrin, ACTH, glucagon and somatostatin. It needs to be remarked that women are more vulnerable to the tumour (60% higher risk of developing such a tumour) [1].

Major symptoms of the disease are connected with neuroglycopenia and together combine the Whipple's triad which comprises: the presence of hypoglycaemia during the fasting period, lowered blood glucose level of 40 mg/dl, and the onset of hypoglycaemia after oral or intravenous administration of glucose. The symptoms are generally expected to appear in the early hours after nightly fasting or heavy exertion. A sudden, seizure-like fit is a telltale sign of insulin overdose. What comes to the fore in the clinical manifestation are the symptoms of parasympathetic nervous system arousal, e.g. heart palpitation, tachycardia, chest pains, shivering, a feeling of apprehension, severe perspiration and salivation. It is often the case that the symptoms of neuroglycopenia pose a serious diagnostic problem, for instance, vision impairment taking the form of diplopia, a feeling of weakness, dizziness, epileptic fits, sleepiness, coma, behavioural disorders, identity change and personality disorders. These may all suggest that the disease has neuropsychiatric grounds. Moreover, nearly 40% of the affected suffer from obesity resulting from excessive appetite. Every sixth person exhibits some complications stemming from the cardiovascular system, which usually take the forms of dilated cardiomyopathy, fluctuations of arterial pressure and irregular heartbeat [3, 4].

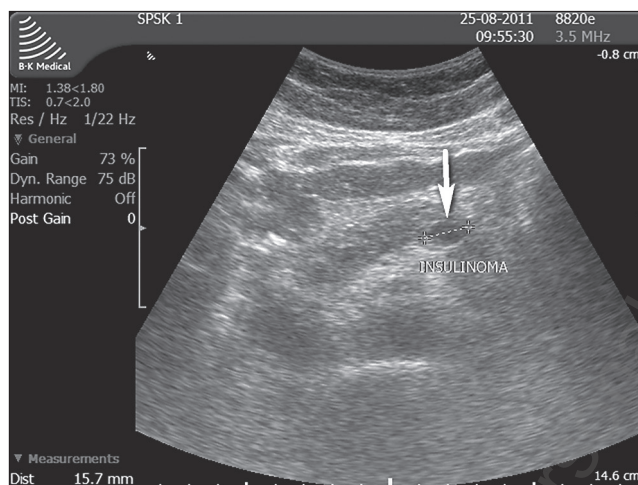
**Diagnostics.** A crucial procedure in the course of insulinoma diagnostics is the fasting test. This period of fasting brings on typical symptoms of Whipple's triad among patients suffering from insulin-secreting tumours. During fasting, the patient must abstain from the consumption of any meals or high-calorie drinks prior to the examination [2]. A 72-hour test is regarded as the golden standard, as specified in the source materials, since the total of 100% of patients with insulinoma will develop the symptoms after this period; however, it can often last for a shorter time [5]. Typically, the fasting starts in the evening. The moment the hypoglycemia symptoms begin to appear, the glucose concentration and insulin concentration should be noted. Afterwards, glucose should be administered intravenously to relieve the symptoms. Healthy individuals subjected to the test will display low glucose levels, while the insulin concentration will be low or indeterminate. Among the patients affected by the tumour, the insulin level will be at an inadequately level in comparison with the low level of glucose. Biochemical criteria should allow for glycaemia measured for a patient with an empty stomach at <45 mg%, insulin concentration >6  $\mu$ IU/ml, C-peptide concentration >0,2 nmol/l and proinsulin at >20 pmol/l. Under the right conditions, the ratio of proinsulin to insulin is placed at <25%, in those suffering from insulinoma this value exceeds 25%. Moreover, the ratio of insulin to glucose within the tumour is disturbed and placed at >0.3 which indicates hyperinsulinism [3, 6].

During laboratory tests, it is not always possible to distinguish insulinoma from non-tumorous pancreatic beta cell hyperplasia, i.e. nesidioblastosis. A medical history interview together with the imaging are supported by the test with intravenous administration of secretin. Patients exhibiting hyperplasia are characterized by an increase of insulinemia as opposed to insulinoma. The presence of antibodies directed against the pancreatic beta cells may also be an indication of its growth rate. Less frequently, provocation tests involving the use of tolbutamide, leucine, arginine, calcium or glucagon are conducted [3, 6].

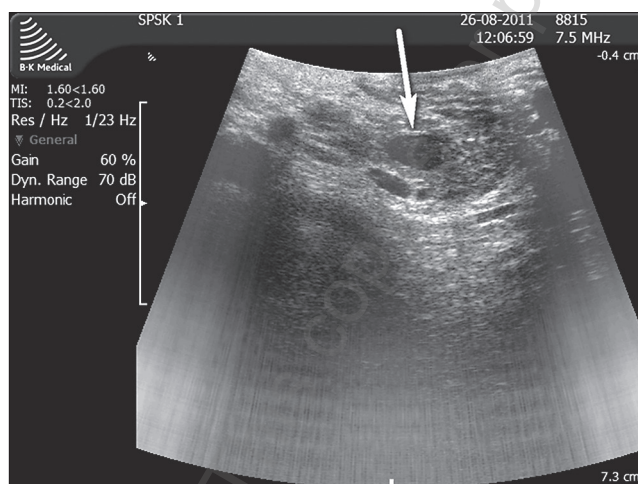
As far as our patient was concerned, the fasting test proved successful. After 20 hours of its duration the symptoms of hypoglycaemia appeared, while the results of the biochemical examination enabled to diagnose insulinoma.

**Imaging tests.** The most fundamental imaging procedures we conduct on patients with suspicion of an insulin tumour is USG examination performed on the abdominal cavity. The primary objective is to locate and identify the tumour. Doppler USG enables evaluation of the vascularization of the tumour; this was carried out in the case of our patient. There are, however, limiting factors that influence the examination, these are: the small size of the tumour, interference with some other organs or obesity. In this respect, the location of the tumour is of crucial importance to the examination ahead since the body and the tail of the pancreas may be difficult captured [4]. In our patient, however, it was possible to expose the tumour at the head and the body of the pancreas. Additionally, the Doppler evaluation provided information on the dense vascularisation of the tumour (Fig. 3, Fig. 4, Fig. 5).

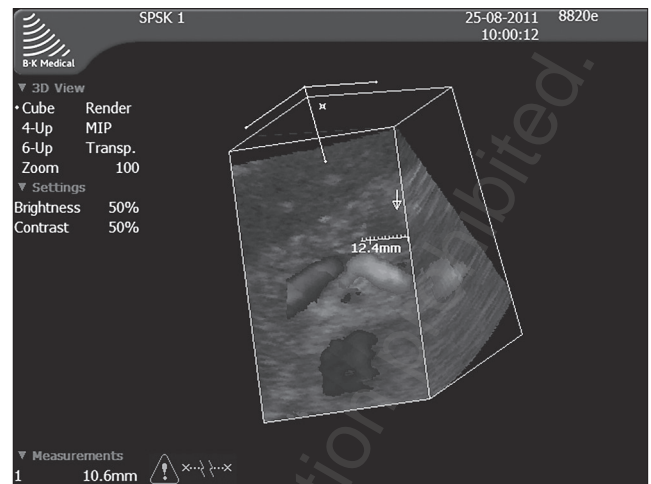
In order to carry out a more thorough assessment we conducted the MRI examination. In the case of insulinoma, MRI is characterized by great sensitivity, estimated at about 65% percent, and according to some sources as much as 90%. MRI allows evaluation of the vascularisation of the tumour,



**Figure 3.** Abdominal Ultrasonography. Neuroendocrine tumour at the edge of the corpus and bottom pancreas



**Figure 4.** Intraoperative ultrasonography. Hypoechoic tumour of about 12-13 mm in size in the corpus of pancreas. Beyond splenic vessels



**Figure 5.** Endocrine tumour of the corpus of pancreas in 3D presentation.

the neighbouring lymph nodes, and enables pinpointing the location of possible metastases. The examination confirmed the good vascularization of the tumour and its location. No metastases were found. The tumour also exhibited features typical of insulinoma under MRI examination, i.e. low-signal intensity on T1-weighted SE images, and high-signal intensity on T2-weighted SE images [4, 7].

The remaining procedures employed preoperatively for insulinoma imaging include: an X-ray computed tomography scan, an EUS examination and angiography procedures [4, 7]. Nevertheless, their application in our case would be unfounded as the USG and MRI image scans were wholly satisfactory.

CT is regarded by some authors as the most basic method for searching for an insulin-secreting tumour. The conventional CT displays low sensitivity to insulinoma. The multiphase spiral CT, however, is characterized by a significantly high diagnostic value. Its sensitivity to the detection of insulinoma can be as much as >80 %, which means that it is very high [4, 7].

EUS is a method which allows the detection of tumours even as small as 2mm in diameter, with a sensitivity of 40-90%. It renders possible a thorough analysis of its location, allows for a meticulous analysis of the local metastases, evaluation of pancreatic lymph nodes, and also the pre-operative tissue diagnosis made with fine needle aspiration (FNA). Unfortunately, it is considered an invasive method, used only in asymptomatic patients with genetically proven MEN-1 syndrome [7, 8].

Angiography is a medical technique which makes it possible to locate insulinoma in 36-91% of cases. A typical picture of an insulin tumour obtained in the process of examination is a single, delomorphous and vascularised mass seen during the arterial phase [4].

The research conducted by Boukhman reveals efficacy as high as 90% of intraoperative ultrasonography which allows the identification of unseen and impalpable tumours. It also demonstrated 75% accuracy in the case of intraoperative palpation [9].

**Treatment.** Patients undergoing a non-pharmacological treatment are advised to avoid lengthy periods of fasting by increasing the frequency of meal consumption, or by adding cornflour to their eating routine [2].

In order to lower the risk of hypoglycaemia, diazoxide is used in the preoperative treatment. Diazoxide standardizes glycaemia and blocks the release of insulin in 60% of patients. The dosing regimen should start from 150-200 mg, being gradually increased to 800 mg/d in several separate dosages. Unfortunately, treatment with diazoxide may entail complications: heart palpitation, excessive hairiness, oedema, nausea and a feeling of discomfort within the abdominal cavity. Other medications could be somatostatin and dilantin. Alternatively, chemotherapy is used in patients with malignant tumours and an improvement can be observed with the use of propranolol, phenytoin, prednisone and glucagon [9, 10].

The surgical treatment of insulinoma is the preferred method of choice. It is currently based upon the enucleation of the tumour, distal pancreatectomy and subtotal pancreatectomy. As far as the patients with the early stage insulinoma are concerned, the treatment is effective in 89% of cases. In patients with a benign tumour, this prognosis can be far more optimistic, attaining up to 96% treatment efficacy. In patients diagnosed with MEN-1, malignant tumours or nesidioblastosis, surgical operations are more often prone to failure, necessitating a further operation in 10% of patients [9].

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