CASE REPORT

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Insulinoma located in the head of the pancreas: Is there an alternative to surgery?

Marcin Balawejder, Katarzyna Skórkowska-Telichowska,
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ABSTRACT

Introduction: Insulinoma is a gastrointestinal tumor, usually benign, which derived from pancreatic beta cells and typically induced by endogenous hyperinsulinism with an incidence rate of 1–4 cases per million inhabitants each year. This case report describes the diagnostic challenges and dilemmas associated with finding optimal treatment for an insulinoma located in the head of the pancreas. **Case Report:** A 41-year-old female was presented with recurrent, nagging headaches, loss of attention and episodes of anxiety accompanied by a feeling of ‘heart palpitation’. Based on the test results, reactive hypoglycemia was diagnosed and further symptomatic treatment was recommended. The patient was admitted again nine years after her initial hospitalization for symptoms of hypoglycemia. Abnormally, high insulin and peptide C secretion was found. Computed tomography (CT) scan revealed a tumor with a size of 1.8x1.3x2.2 cm located within the uncinate

process of the pancreas. Pancreatoduodenectomy was recommended. However, the patient refused surgery. She was given somatostatin analogues leading to a satisfactory clinical effect. Computed angiotomography was done which confirmed the presence of an abundantly vascularized tumor within the head of the pancreas. Embolization with histoacryl glue was performed. Due to the ineffectiveness of embolization, treatment with short-acting and then long-acting synthetic somatostatin analogues was reintroduced. A follow-up CT scan conducted six months after the procedure revealed regression of tumor size. **Conclusion:** Treatment of choice for insulinoma is surgery, but conservative treatment is recommended when surgery is impossible or contraindicated. Afferent vessel embolization is a safe treatment option. Chemotherapy may be an option for inoperable, malignant tumors.

Keywords: Insulinoma, Hypoglycemia, Somatostatin analogues, Afferent vessel embolization

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INTRODUCTION

Insulinoma, a tumor which is derived from pancreatic beta cells, is the most common cause of hypoglycemia induced by endogenous hyperinsulinism [1]. Its incidence rate is 1–4 case(s) per million inhabitants each year. It is usually a benign tumor that may occur as a part of a

syndrome known as MEN 1 (multiple endocrine neoplasia 1) [2].

Clinical manifestations include the Whipple's triad. These include hypoglycemic symptoms such as sweating, shivering, heart palpitation, but mainly consists of the symptoms of neuroglycopenia such as headaches, visual disturbances, confusion, drowsiness, speech disturbance, behavioral abnormalities and tremors. Insulinoma is confirmed by reduction in fasting glucose levels <40 mg/dL (2.2 mmol/L), which typically resolves after carbohydrate administration [3]. Laboratory examinations show inappropriately high concentrations of insulin (>36 pmol/L or 6 IU/L) relative to glucose levels, C peptide >200 pmol/L and proinsulin >5 pmol/L during the fasting test of up to 72 hours [1, 3].

CASE REPORT

In 2001, a 41-year-old female was admitted to the Department of Endocrinology of the 4th Military Clinical Hospital in Wrocław for non-specific complaints. These included recurrent, nagging headaches, loss of attention, episodes of anxiety accompanied by a feeling of 'heart palpitation' as well as trembling of her hands and increased sweating. These symptoms typically appeared within three hours of a meal and resolved up to 30 minutes after taking simple carbohydrates. The patient's previous laboratory examination showed a reproducible decrease in blood glucose levels to a minimum of 20 mg/dL, which correlated with her symptoms. The patient had no significant clinical history and had not been medically treated in the past.

During her hospitalization, a combined evaluation of her blood glucose, insulin, and C peptide levels was carried out (Table 1). Thyroid and adrenal gland function were also assessed. Based on the test results, reactive hypoglycemia was diagnosed and further symptomatic treatment was recommended.

The patient was admitted again to the Department of Endocrinology nine years after her initial hospitalization. This time her medical history included more pronounced symptoms of hypoglycemia— they were more frequent, more severe and more difficult to reverse, accompanied by symptoms of neuroglycopenia occurring several times a week. The patient also reported an episode of syncope with a short-term loss of consciousness. In between her hospitalizations, she had been treated for stage II arterial hypertension (according to WHO classification) for several years. The treatment included therapy with perindopril, indapamide and metoprolol succinate.

Physical examination at admission revealed obesity (BMI 34.5 kg/m²). The combined evaluation of blood glucose, insulin, and C peptide levels were repeated. The patient was subjected to a 5-hour oral glucose tolerance test with 75 grams of glucose, a fasting test and an assessment of adrenal and thyroid gland function (Table 1).

The results showed abnormally high insulin and peptide C secretion compared to glucose levels and normal functioning of the thyroid and adrenal glands.

Supplementary diagnostic imaging of the abdominal cavity using an ultrasound scan revealed no abnormalities, apart from signs of hepatic steatosis. Computed tomography (CT) scan revealed a tumor with a size of 1.8x1.3x2.2 cm located within the uncinate process of the pancreas (Figure 1). The lesion displayed intensive contrast enhancement in the arterial phase of the examination, which was characteristic of insulinomas and associated with their abundant vascularization.

Figure 1: The initial computed tomography scan with cross sections in three basic dimensions and a volume rendering (bottom left corner) revealed a tumor within the head of the pancreas, which was adjacent to the common bile duct and showing intensive contrast enhancement.

The patient was pre-approved for surgery. Pancreatoduodenectomy was recommended because the lesion was localized within the head of the pancreas, in the proximity of the common bile duct and the inferior vena cava, as well as the abundant vascularization of the tumor. However, the patient did not give her formal consent to the procedure. Therefore, treatment with short-acting, and later long-acting synthetic somatostatin analogs were started, leading to a satisfactory clinical effect - no hypoglycemia incidents were observed (Table 2).

Pharmacological therapy was discontinued approximately half a year later. Symptoms of hypoglycemia reoccurred within three months following treatment discontinuation. As continuation of pharmacological treatment was impossible and the patient still refused to give her consent to surgery, investigation of the tumor blood supply and obliteration of the supplying vessels was suggested as an alternative treatment.

Table 1: Clinical evaluation of patient before treatment.

THYROID HORMONES											
Hospitalization									1 st day	2 nd day	
TSH (μIU/mL, reference values 0.27–4.20)									0.6	0.994	
fT4 (ng%, reference values 0.93–1.7)									1.3	1.42	
DAILY GLUCOSE, INSULIN AND C-PEPTIDE PROFILES											
Time	3 a.m.	7 a.m.	10 a.m.	3 p.m.	4 p.m.	8 p.m.	12 p.m.				
Hospitalization	1 st day	2 nd day	1 st day	2 nd day	1 st day	2 nd day	1 st day	2 nd day	1 st day	2 nd day	
Glucose (ng % , fasting reference values 74–100)	-	-	81	-	26	-	30	44	39	-	
Insulin (μIU/ mL, fasting reference values 3.21–16.32)	7.1	5.9	35.4	-	139.9	-	181.9	15.5	-	17.1	171.4
C-peptide (ng/ mL, fasting reference values 0.8–4.2)	3.6	2.7	5.4	-	11.1	-	11.6	6.3	-	6.4	12.5
											4.5
											-
STATIC ASSESSMENT OF GLUCOCORTICOID LEVELS											
Time				7 a.m.						8 p.m.	
Hospitalization				1 st day	2 nd day					1 st day	2 nd day
Cortisol (nmol/L, reference values for 7 a.m. 171–536, for 8 p.m. 64–340)				633.8	773.4					81.5	71.1
ACTH (pg/mL, reference values 0.0–46.0)				49.6	75.7					-	7.7
Hospitalization				1 st day						2 nd day	

Table 1: (Continued)

24-hour urine cortisol level (nmol/24 h, reference values 100–379)												-	1724.8	
GLYCATED HEMOGLOBIN														
Hospitalization		1 st day		2 nd day										
HbA1c (%; reference values 4.0–6.0)		8.9		4.7										
PROLONGED ORAL GLUCOSE TOLERANCE TEST WITH 75 grams OF GLUCOSE														
Time		0 hour		1 hour		2 hours		3 hours						
Hospitalization		1 st day		2 nd day		1 st day		2 nd day		1 st day		2 nd day		
glucose (ng %, fasting reference values 74–100)		-		39		-		206		-		115		
Insulin (μIU/ml, fasting reference values 3.21–16.32)		-		24.3		-		81.3		-		101.0		
INSULIN-INDUCED HYPOGLYCEMIA TEST														
Time		0		30 minutes		60 minutes		90 minutes		4 hours		5 hours		
		Test started at the blood glucose level of 40 mg/dL												
Hospitalization		1 st day		2 nd day		1 st day		2 nd day		1 st day		2 nd day		
Cortisol (nmol/l, reference values for 7 a.m. 171–536, for 8 p.m. 64–340)		-		592.5		-		330.5		-		220.8		
ACTH (pg/ml, reference values 0.0–46.0)		-		20.1		-		7.2		-		7.7		
FASTING TEST														
Time		7 a.m.		10 a.m.		2 p.m.		4 p.m.						
Hospitalization		1 st day		2 nd day		1 st day		2 nd day		1 st day		2 nd day		

Table 1: (Continued)

Glucose (ng %, fasting reference values 74–100)	-	64	-	142	-	47	-	33	-
Insulin (μIU/mL, fasting reference values 3.21–16.32)	-	24.0	-	179.0	-	42.9	-	-	-
Hospitalization	1 st day				2 nd			413.9	-
Cortisol (nmol/L, reference values for 7 a.m. 171–536, for 8 p.m. 64–340)	-				655.0				
CHROMOGRANIN A									
Hospitalization	1 st day				2 nd				
Chromogranin A (mg/mL, reference values 0.0–100.0)	-				24.9				

Table 2: Clinical evaluation of patient after treatment.

DAILY GLUCOSE, INSULIN AND C-PEPTIDE PROFILES									
Time	7 a.m.	10 a.m.	3 p.m.	8 p.m.	embolization	synthetic somatostatin analogues	embolization	synthetic somatostatin analogues	embolization
After treatment	synthetic somatostatin analogues	synthetic somatostatin analogues	synthetic somatostatin analogues	synthetic somatostatin analogues	embolization	synthetic somatostatin analogues	embolization	synthetic somatostatin analogues	embolization
Glucose (ng %, fasting reference values 74–100)	114	123	128	146	48	37	32	32	32
Insulin (μIU/mL, fasting reference values 3.21–16.32)	4.9	27.7	22.2	35.2	107.9	44.9	89.1	89.1	89.1
C-peptide (ng/mL, fasting reference values 0.8–4.2)	1.99	5.49	6.03	6.83	10.50	7.81	11.30	11.30	11.30
PROLONGED ORAL GLUCOSE TOLERANCE TEST WITH 75 grams OF GLUCOSE during treatment with synthetic somatostatin analogues									
Time	0	1 hour	2 hours	3 hours	4 hours	5 hours			
Glucose (ng %, fasting reference values 74–100)	86	184	90	66	70	91			
Insulin (μIU/mL, fasting reference values 3.21–16.32)	7.70	97.3	3.4	36.1	4.3	4.3			
FASTING TEST during treatment with synthetic somatostatin analogues									
Time	7 a.m.	10 a.m.	12 a.m.	2 p.m.	4 p.m.	6 p.m.	9 p.m.	12 p.m.	
Glucose (ng %, fasting reference values 74–100)	100	96	96	95	95	99	98	103	

Table 2: (Continued)

Insulin (μIU/mL, fasting reference values 3.21–16.32)	8.7	3.8	4.8	1.6	3.6	<0.2	2.0	2.0
GLYCATED HEMOGLOBIN								
After treatment								
synthetic somatostatin analogues								
HbA1c (% reference values 4.0–6.0)		6.1				embolization		
						5.2		

Computed angiotomography was performed at the Clinical Department of Proctological and Minimally Invasive Surgery, Medical University of Wrocław in order to assess therapeutic possibilities for tumor embolization. This examination confirmed the presence of an abundantly vascularized tumor within the head of the pancreas (size 1.5x1.2x2.1 cm) which was adjacent posteriorly and laterally on the right with the common bile duct, posteriorly with the inferior vena cava and supplied by the small branches of the superior mesenteric artery and a very small branch of the gastroduodenal artery. The diameter of the examined vessels made it impossible to precisely investigate their location. Therefore, it was decided to carry out a selective contrast-enhanced computed angiotomography following afferent artery catheterization. This examination revealed the tumor's supplying vessels, which originated from the first branch of the superior mesenteric artery. Embolization with histoacryl glue was performed. A control arteriography revealed the obliteration of the supplying vessels and the tumor, which did not show any contrast enhancement.

Neither clinical nor laboratory indicators of hypoglycemia were observed directly after the procedure.

Within five months following the procedure, the patient had a reoccurrence of hypoglycemia symptoms. Her blood glucose level had decreased to approximately 40 mg/dL. Further examinations revealed increased insulin levels, which showed a correlation with observed hypoglycemia (Table 2).

Due to the ineffectiveness of embolization, treatment with short-acting and then long-acting synthetic somatostatin analogs were reintroduced, accompanied

by a low glycemic index diet. The achieved therapeutic effect was satisfactory (glucose level: 51–67 mg/dL at 7 a.m., 115–143 mg/dL at 10 a.m., 79–89 mg/dL at 3 p.m., and 95–119 mg/dL at 8 p.m.).

A follow-up CT scan conducted six months after the procedure revealed the presence of embolic material in the inferomedial portion of the tumor and the regression of its size (Figure 2). Tumor volume reduction from 5 mL to 2.5 mL was confirmed using tumor-monitoring software; this reduction correlates with the suboptimal effect of the earlier embolization procedure.

At present, the patient is continuing her treatment with the long-acting synthetic somatostatin analog with satisfactory clinical consequences. She is also being monitored for the long-term effects of limiting arterial blood supply to the tumor. If the desired effects are not achieved, pharmacotherapy may be continued or the Kausch–Whipple procedure may be performed. Additionally, a second embolization may also be considered.

DISCUSSION

Diagnostic imaging in insulinoma can often be difficult due to the small size of the tumor which is <2 cm diameter in 80% of cases. This is why multiple imaging techniques are used [2].

Surgery is the treatment of choice for insulinoma, while the choice of surgical procedure depends on tumor size, location and histopathological characteristics. Laparoscopic tumor resection is recommended in tumors located in the body or tail of the pancreas. Classic surgery is performed, if exact tumor location is impossible to determine, or when multiple lesions are suspected [4]. It is then possible to use the intraoperative ultrasound scan and to perform gradual pancreatectomy with the intraoperative insulin level measurement in order to assess the extent of the surgery. When the lesion is located within the head of the pancreas, it is usually necessary to carry out a pancreatoduodenectomy, an extensive surgical procedure associated with a high risk of intraoperative and postoperative complications, significantly decreasing the quality of life, particularly in patients with neuroendocrine tumors [5]. If the tumor is malignant, total pancreatectomy and lymphadenectomy can be performed [1].

Conservative treatment is recommended when surgical intervention is impossible due to the lack of consent or patient's health status, or when radical treatment is contraindicated due to advanced disease. Somatostatin is a natural inhibitor of pancreatic, intestinal and pituitary hormones and somatostatin analogues are used to prevent hypoglycemia. While observational studies have confirmed the efficacy of glycemia control using long-acting somatostatin analogues, this treatment is only effective in patients whose tumors contain somatostatin receptors [6], i.e., approximately 50% of all insulinomas.

Figure 2: A follow-up computed tomography scan revealed tumor volume reduction; a small, hyperdense focus within the lower pole of the tumor, visible in the sagittal section, apparently corresponded to the embolic material.

Short-acting somatostatin analogues are used solely to stabilize a patient's condition and assess their therapeutic response to a drug. Diazoxide (not available in Poland) can be used as an alternative treatment but it causes edema, renal damage and hirsutism [3]. Interferon alpha can also be used as a part of conservative treatment. In case of inoperable, malignant tumors, chemotherapy using 5-fluorouracil and streptozotocin are viable options [1].

Single case reports describe afferent vessel embolization, a method of neuroendocrine tumor treatment which reduces tumor mass and relieves or leads to a complete resolution of hypoglycemic symptoms in an insulinoma [7]. It is sometimes used also as the preoperative strategy for tumor mass reduction before an extensive and aggressive surgery [8]. In the latter case it is a safe treatment method, especially when embolization involves a selectively chosen vessel. It shortens the duration of the consecutive surgery and reduces blood loss during the procedure [9, 10].

CONCLUSION

While the treatment of choice for insulinoma is surgery, conservative treatment is recommended when surgery is impossible or contraindicated. Afferent vessel embolization is a safe treatment option, while chemotherapy may be a treatment option for inoperable, malignant tumors.

Author Contributions

Marcin Balawejder – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Katarzyna Skórkowska-Telichowska – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Tomasz Kuniej – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Renata Tuchendler – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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