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Nesidioblastosis coexisting with non-functioning islet cell tumour in an adult

Przetrwała hipoglikemia hiperinsulinemiczna współistniejąca z nieaktywnym wyspiakiem trzustki

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Abstract

The most common cause of hyperinsulinaemic hypoglycaemia in adult is insulinoma. Although nesidioblastosis is a rare but well-recognised disorder of persistent hypoglycaemia in infants, it is extremely rare in adults.

We present a case of a 59-year-old woman with small neuroendocrine tumour of the tail of the pancreas, diagnosed by CT scans and MRI, and hypoglycaemic syndrome. Laparoscopic distal pancreatectomy was performed, and pathologic examination showed a well-differentiated, non-functioning endocrine tumour of the pancreas and diffuse nesidioblastosis in the remnant gland. In the early postoperative period, recurrent hypoglycaemia occurred in spite of oral diazoxide therapy. Plasma proinsulin levels were extremely high. 18F-DOPA positron emission tomography showed a pathologic uptake of tracer in the head and the uncinate process of the pancreas. Subtotal pancreatectomy was suggested but the patient refused operation: she is taking diazoxide 100 mg three times daily.

Coexistence of nesidioblastosis with a neuroendocrine tumour makes preoperative diagnosis and management of severe hypoglycaemia more difficult. Nesidioblastosis should be considered in differential diagnosis of hypoglycaemic syndrome, but histological examination is necessary for a definitive tissue diagnosis. **(Endokrynol Pol 2015; 66 (4): 356–360)**

Key words: *diazoxide; hypoglycaemia; nesidioblastosis; neuroendocrine tumour; pancreas; pancreatectomy*

Streszczenie

Najczęstszą przyczyną hipoglikemii hiperinsulinemicznej u osób dorosłych jest insulinoma. Chociaż przetrwała hipoglikemia hiperinsulinemiczna to rzadkie, lecz łatwo rozpoznawalne zaburzenie przetrwałej hipoglikemii u noworodków, bardzo rzadko występuje u osób dorosłych.

Autorzy badania przedstawiają przypadek 59-letniej kobiety z niewielkim guzem neuroendokrynnym ogona trzustki, zdiagnozowanym dzięki tomografii komputerowej oraz rezonansowi magnetycznemu, oraz zespołem hipoglikemicznym. Wykonano laparoskopową dystalną pankreatektomię, a badanie patologiczne wykazało wysoko zróżnicowanego, nieaktywnego, endokrynnego wyspiaka trzustki oraz rozlaną przetrwałą hipoglikemię hiperinsulinemiczną w pozostałej części gruczołu. We wczesnym okresie pooperacyjnym wystąpiła nawracająca hipoglikemia, mimo stosowania doustnego leczenia diazoksydem. Stężenie proinsuliny w osoczu był bardzo wysoki. Pozytonowa tomografia emisyjna z 18F-DOPA wykazała patologiczną absorpcję znacznika w głowie i wyrostku haczykowatym trzustki. Sugerowano subtotalną pankreatektomię, lecz pacjentka nie zgodziła się na operację: przyjmowała dawkę 100 mg diazoksydu trzy razy dziennie.

Współistnienie przetrwałej hipoglikemii hiperinsulinemicznej z nowotworem neuroendokrynnym utrudnia diagnostykę przedoperacyjną i leczenie ciężkiej hipoglikemii. Przetrwała hipoglikemia hiperinsulinemiczna powinna być brana pod uwagę w diagnozie różnicującej zespół hipoglikemiczny, lecz badanie histologiczne jest niezbędne do definitywnej diagnozy tkanek. **(Endokrynol Pol 2015; 66 (4): 356–360)**

Słowa kluczowe: *diazoksyd; hipoglikemia; przetrwała hipoglikemia hiperinsulinemiczna; nowotwór neuroendokrynny; trzustka; pankreatektomia*

Introduction

Hyperinsulinaemic hypoglycaemia in adults is commonly caused by insulinoma or exogenous insulin administration [1]. However, rare cases are associated with diffuse islet cell hyperplasia arising from ductal epithelium, a condition known as nesidioblastosis.

Nesidioblastosis is the primary cause of persistent hyperinsulinaemic hypoglycaemia in infants, but it accounts for only 0.5% to 7% of all cases of hyperinsulinaemic hypoglycaemia in adults [2]. Moreover, while infant nesidioblastosis is mainly caused by mutations of genes encoding subunits of pancreatic ATP-sensitive potassium channel [3, 4], the cause of adult nesidioblastosis is still unknown. The majority of cases are associated with previous bariatric surgery, suggesting a possible reactive process involving glucagon-like peptide 1-induced islet cell proliferation, which could

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promote or unmask a beta-cell defect leading to its hyperplasia [5, 6] Here we report a rare case of non-insulinoma hypoglycaemia syndrome in a middle-aged woman, who presented with a small non-functioning neuroendocrine tumour in the tail of the pancreas coexisting with nesidioblastosis. A review of literature was also performed.

Case report

A 59-year-old woman was referred to another hospital for severe hypoglycaemia in March 2012; since then, she reported recurrent episodes of hypoglycaemia of unknown origin. The medical history of the patient was remarkable for appendectomy and hysterectomy several years ago, and a recovery in ICU for Staphylococcal sepsis in February 2012. She did not undergo bariatric surgery and she did not have a positive familiar history for diabetes or pancreatic diseases.

72-hour fasting test revealed symptomatic hypoglycaemia with a blood glucose level of 42 mg/dL after a fasting time of 38 hours. Oral Glucose Tolerance Test (OGTT) provoked hypoglycaemia (54 mg/dL) 240 minutes after glucose challenge. Her low fasting plasma glucose level was accomplished by low levels of insulin and C-peptide, but high plasma levels of pro-insulin (169–183 pmol/L; normal level 0.7–8.3 pmol/L). In December 2012 contrast enhanced computed tomography of the abdomen (CT) revealed a small hypodense lesion in the tail of the pancreas. Magnetic resonance imaging (MRI) of the abdomen showed a 6-mm contrast-enhanced lesion in the tail of the pancreas, suggestive of a neuroendocrine tumour (possible insulinoma) (Fig. 1). Oral diazoxide therapy was started, and the patient was advised to eat small, low-carbohydrate meals. Finally, in January 2013 the patient underwent laparoscopic surgical exploration. Intraoperative ultrasonography confirmed a 6-mm lesion in the tail of the pancreas, close to splenic vessels. Laparoscopic distal pancreatectomy and splenectomy was carried out. Histological examination showed a well-differentiated endocrine tumour of the pancreas (6 mm in diameter) associated with diffuse nesidioblastosis in the remnant gland (Fig. 2A). Immunohistochemistry examination of the pancreas showed positive reaction for Chromogranin A (Dako, rabbit polyclonal antibody, dilution 1:100) (Fig. 2B) both in the tumour and nesidioblastosis, positive reaction for insulin (Novocastra, mouse monoclonal antibody clone 2D11-H5, dilution 1:100) (Fig. 2C) and proinsulin (Beta Cell Biology Consortium; mouse monoclonal antibody GS-9A8, dilution 1:1000) (Fig. 2D) were shown in nesidioblastosis, but not in the tumour. Mib1 labelling index was 1%. Postoperative recovery was complicated by the onset of abdominal fluid collection that required laparoscopic drainage. Following surgery the patient developed several hypoglycaemic episodes and she was discharged with oral diazoxide therapy (Diazoxide 50 mg twice daily).

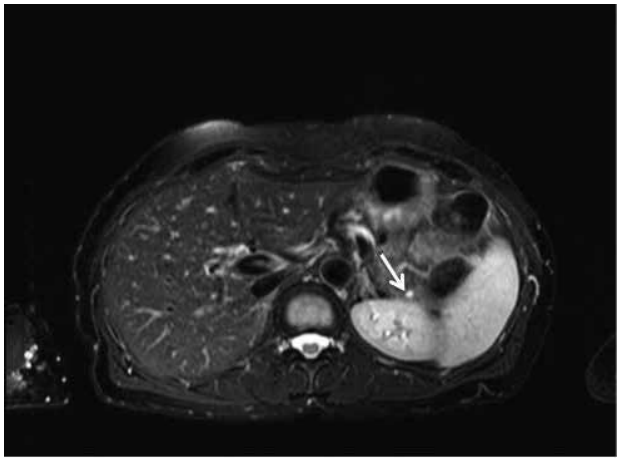

Figure 1. *Magnetic resonance imaging of the abdomen showing a 6-mm, contrast-enhanced lesion in the tail of the pancreas (arrow)*

Rycina 1. *Rezonans magnetyczny jamy brzusznej ukazujący 6-milimetrową, podkreśloną kontrastem zmianę w ogonie trzustki (strzałka)*

Despite medical treatment, recurrent hypoglycaemic episodes occurred, and the patient was referred to our Department. In June 2013, 72-hour fasting test showed symptomatic hypoglycaemia with a blood glucose level of 45 mg/dL after a fasting time of 32-hours; oral glucose tolerance test provoked hypoglycaemia (50 mg/dL) 300 minutes after glucose challenge. Plasma pro-insulin levels were extremely high. 18F-dihydroxylalanine (DOPA) PET with CT acquisition displayed a pathologic uptake of tracer in the head and the uncinate process of the pancreas (Fig. 3). Subtotal pancreatectomy was suggested but the patient decided to continue with medical therapy. After one year of operation, the patient is well, asymptomatic, and normoglycaemic: she is taking diazoxide 100 mg three times daily, without evidence of pancreatic exocrine insufficiency. The last contrast-enhanced abdominal ultrasonography, performed in June 2014, did not reveal any pancreatic lesion.

Discussion

Diagnosis of nesidioblastosis is challenging, and it is rarely made before surgical exploration [7]. Clinical signs and symptoms could mimic those of insulinoma, which was firstly suspected in our patient. In fact, our patient presented with a small non-functioning neuroendocrine tumour in the tail of the pancreas, making preoperative diagnosis more confusing. Although the coexistence of pancreatic endocrine neoplasm with nesidioblastosis is extremely rare, it has been previously

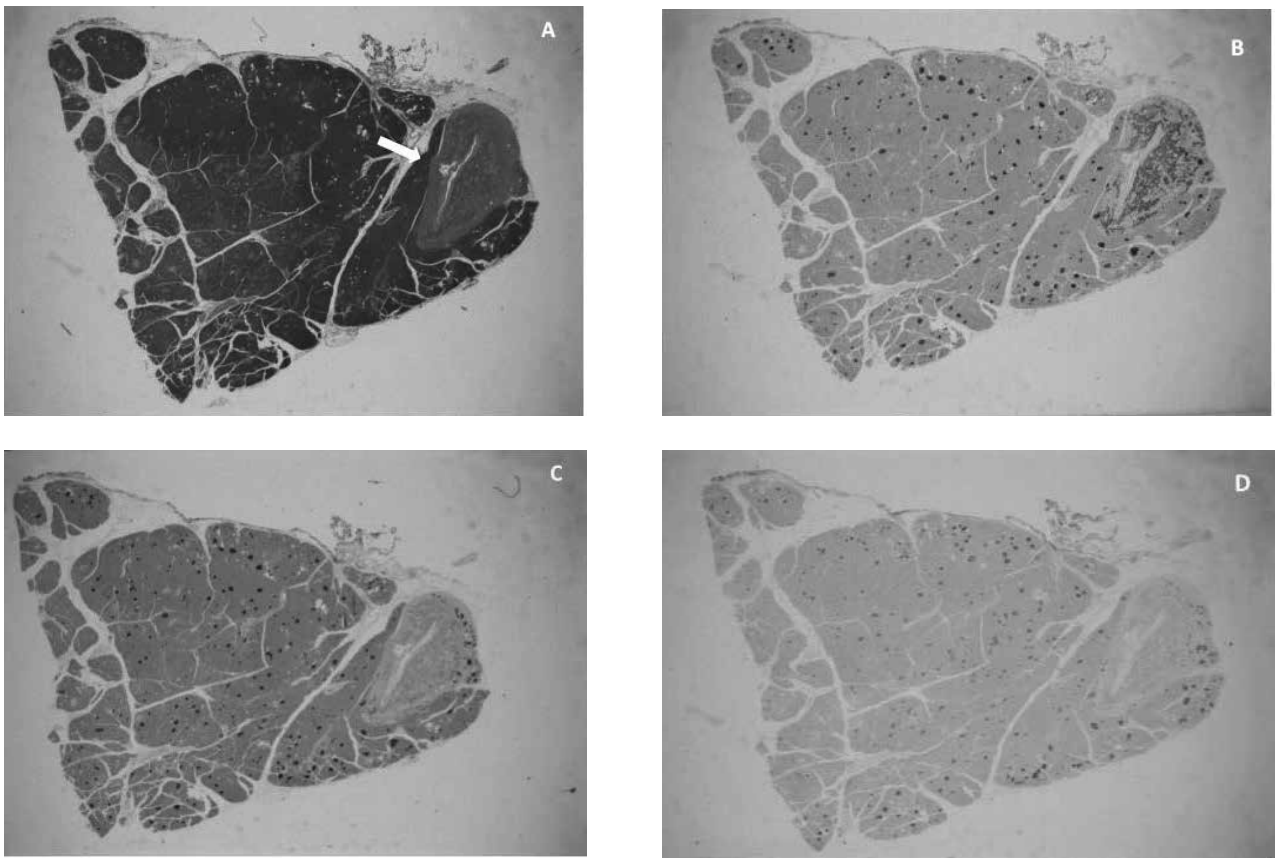

Figure 2A. *Microscopic examination showing a small neuroendocrine tumour (arrow) and diffuse nesidioblastosis in the remnant pancreas (H&E; 10×).* **B.** *Immunostaining positive for chromogranin-A both in tumour and nesidioblastosis.* **C.** *Immunostaining for insulin showing diffuse positivity in nesidioblastosis and marginal positivity in the tumour.* **D.** *Immunostaining for proinsulin showing diffuse positivity in nesidioblastosis and negativity in the tumour*

Rycina 2A. *Badanie mikroskopowe ilustrujące niewielki nowotwór neuroendokrynny (strzałka) i rozlaną przetrwałą hipoglikemię hiperinsulinemiczną w pozostałej części trzustki (H&E; 10×).* **B.** *Dodatnie zabarwienie immunologiczne dla chromograniny A zarówno dla nowotworu, jak i przetrwałej hipoglikemii hiperinsulinemicznej.* **C.** *Zabarwienie immunologiczne dla insuliny, ilustrujące rozległą dodatnią przetrwałą hipoglikemię hiperinsulinemiczną i marginalną dodatniość w nowotworze.* **D.** *Zabarwienie immunologiczne dla proinsuliny, ilustrujące rozległą dodatnią przetrwałą hipoglikemię hiperinsulinemiczną i ujemność w nowotworze*

reported [8–18]. In the literature review we collected a total of 13 patients (our included) which presented islet cell tumor associated with nesidioblastosis [8–18] (Table I). There were 10 females and 3 males with a mean age of 43.2 ± 9.1 years. Eleven patients presented severe hypoglycaemia syndrome, one had type 2 diabetes, and one was asymptomatic. All patients underwent pancreatic resection: distal pancreatectomy, 4 subtotal pancreatectomy, 2 pancreaticoduodenectomy (3 patients had more than 1 operation). Eight patients had coexisting insulinomas (multiple in 2 and malignant in 1 patient), while 5 showed a non-functioning islet cell tumour: one patient had α cell hyperplasia and multiple microglucagonomas [16]. Four patients required medical treatment, such as diazoxide (n = 3) or octreotide (n = 1). In all but one patient no further episodes of severe hypoglycaemia occurred; two patients became diabetic.

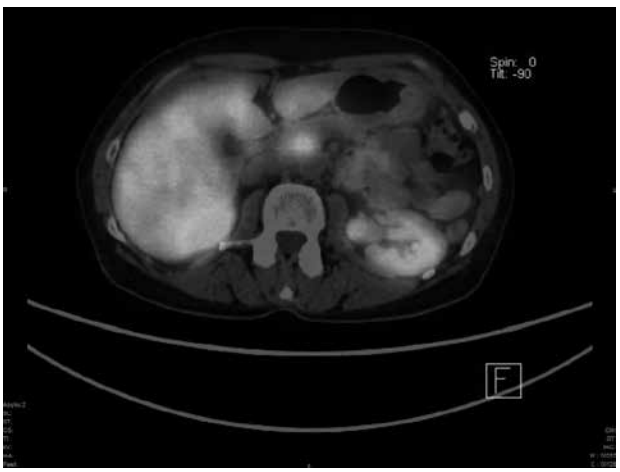

Figure 3. *18F-DOPA PET showing a pathologic uptake of the radiotracer in the head of the pancreas*

Rycina 3. *Pozytonowa tomografia emisyjna z18F-DOPA ilustrująca patologiczną absorpcję radioznacznika w głowie trzustki*

Table I. *Clinicopathological features of Nesidioblastosis and coexisting islet cell tumour published in literature*

Tabela I. *Cechy kliniczno-patologiczne przetrwałej hipoglikemii hiperinsulinemicznej i współistniejącego wyspiaka trzustki opublikowane w literaturze*

		Sex	Age	Tumor	Symptoms	Treatment		Outcome (months)
						Surgery	Medical	
Leong et al. [8]	1980	F	40	Insulinoma	Hypoglycaemia	DP	No	NED (30)
Madeira et al. [9]	1986	F	34	Insulinoma	Hypoglycaemia	DP + PD	No	Diabetes (NA)
White et al. [10]	2000	F	32	NET	Hypoglycaemia	DP	No	NED (12)
Zhao et al. [11]	2001	M	34	NET + IPMN	Hypoglycaemia	DP	No	NED (24)
Kaczirek et al. [12]	2003	F	51	Insulinoma	Hypoglycaemia	DP + PD	No	Diabetes (24)
Service et al. [13]	2005	NA	29	Multiple insulinomas	Hypoglycaemia	DP	No	NED (20)
Dissanayake et al. [14]	2007	F	NA	Insulinoma	Hypoglycaemia	STP	No	NED (NA)
Rosman et al. [15]	2007	M	38	Malignant insulinoma	Hypoglycaemia	DP +RF	Diazoxide	NA
Bright et al. [16]	2008	F	37	Insulinoma	Hypoglycaemia	DP	No	NED (30)
Yu et al. [17]	2008	F	35	NET	No	PD	Octreotide	NED (36)
Gupta et al. [18]	2013	F	60	Multiple insulinomas	Hypoglycaemia	E + STP	Diazoxide	NED (12)
Choi et al. [19]	2013	F	50	NET	Diabetes type II	PD	Hypoglycaemic drugs	NED (40)
Present	2014	F	43	NET	Hypoglycaemia	DP	Diazoxide	NED (12)

DP — distal pancreatectomy; PD — pancreaticoduodenectomy; SPT — subtotal pancreatectomy; E — enucleation; NED — not evidence of disease; NA — not available; NET — Non-functioning neuroendocrine tumour; IPMN — intraductal papillary mucinous neoplasm

Genetic defects involving the subunits of the ATP-sensitive potassium channel in pancreatic beta cells are known to be responsible for development of persistent hyperinsulinaemic hypoglycaemia of infancy [2], and some of them could also be associated with development of the disease in adults. Despite this, pathogenesis of nesidioblastosis in adults is still unclear, even if it may be associated with bariatric surgery and its metabolic changes, especially in patients who underwent a gastric bypass with Roux-en-Y reconstruction [19].

Clinical features of nesidioblastosis are represented by postprandial hyperinsulinaemic hypoglycaemia, negative 72-hour fast, negative pre-operative localisation studies for insulinoma, and positive selective arterial calcium injection (SACI) test [20, 21]. In fact, preoperative differentiation of nesidioblastosis from insulinoma is difficult because conventional radiologic testing (CT, MRI) is not reliable: its sensitivity for an insulinoma is only 50% to 80%, and false positive results occur [19].

Use of SACI test with hepatic venous sampling can demonstrate hyperactive beta-cell activity; nesidioblastosis is suspected if calcium injection into all pancreatic vessels results in insulin release from the entire pancreas [21]. In our case, SACI-test was not performed because radiologic imaging was highly suggestive for the diagnosis of insulinoma.

New diagnostic options, such as 18F-DOPA PET, could be useful to localise a suspected insulinoma or congenital hyperinsulinaemia, but its value in differentiating insulinoma from nesidioblastosis has not yet been demonstrated [22, 23].

Treatment strategies for nesidioblastosis are represented by medical therapy with diazoxide or octreotide, and pancreatectomy. The extent of pancreatic resection is controversial: nowadays, distal pancreatectomy is considered as the treatment of choice. This procedure results in a cure in about half of the patients, with no need for further medications, and an additional 19% of patients being normoglycaemic, taking medications. Insulin-dependent diabetes occurs in only 8% of cases. Near-total (90% to 95%) pancreatectomy would seem a logical procedure considering the diffuse nature of the islet cell disease; however, 40% of patients who underwent this operation developed insulin-dependent diabetes mellitus, and exocrine pancreatic insufficiency occurs as well [20, 24].

Treatment options for recurrent hypoglycaemia after surgery are limited; patients could be advised to eat six small, low-carbohydrate meals daily, or they can be successfully treated with diazoxide or octreotide. In a limited percentage of cases, resection of the remaining pancreatic gland is necessary.

Conclusions

Although adult nesidioblastosis is a rare pathology, it should be kept in mind in differential diagnosis of severe hypoglycaemia syndrome. Conventional ra-

diologic testing is not very reliable, especially when an association with a neuroendocrine tumour exists. Consequently, diagnosis is only possible after surgical exploration and histological examination of the resected pancreas.

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