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Patient with multifocal pancreatic insulinoma: a rare presentation of functional pancreatic neuroendocrine neoplasm

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Insulinoma is a type of neuroendocrine tumour with an incidence of 1—4 cases per million. Multiple insulinomas constitute less than 10 % of all insulinomas. Surgery is the treatment of choice for insulinoma. The operation can be done with an open or laparoscopic approach, with cure rates ranging from 77 % to 100 %. Pancreatic resection is recommended for tumours larger than 2 cm in size, while enucleation is advised for lesions smaller than 2cm if the tumour is at least 2—3 mm away from the main pancreatic duct to prevent the formation of a fistula. For better intraoperative localization of lesions, bimanual palpation together with intraoperative ultrasonography (IOUS) is advised. Palpation alone has 70 % sensitivity, but together with IOUS, it reaches 85—95 %

A young female patient in her late 20s with non-specific complaints and a medical history of epilepsy dating back to the age of 17 underwent a physical examination. Blood test results indicated severe hypoglycemia, and magnetic resonance imaging (MRI) revealed an 11-mm neoplasia in the body of the pancreas. A 72-hour fasting test confirmed the diagnosis of insulinoma, and the patient underwent laparoscopic surgery. IOUS was done for the precise localization of the lesion, and another tumour in the pancreatic tail was found. A spleen-preserving laparoscopic distal pancreatectomy was performed. Histologic reports confirmed multifocal Grade 1 insulinoma. The postoperative course was uneventful. After 4 months of follow-up, computed tomography (CT) was done, and there were no signs of recurrence of insulinoma, pancreatic pseudocysts, or other signs of postoperative complications. Since the operation, the patient has not had any episodes of hypoglycemia or seizures.

The wide spectrum of symptoms, which are not specific to insulinomas, in particular seizures, can make it difficult to establish a correct diagnosis and can be mistaken for other psychiatric or neurologic disorders. This case clearly shows the advantages of IOUS-guided surgery in achieving better visualization and outcomes. After enucleation of the smaller lesion without the use of IOUS, other insulinomas would be missed and left in place because they were located deeply in the parenchyma. Simple visualization and palpation would not be enough.

Keywords
multiple insulinomas, surgical treatment, intraoperative ultrasonography, seizures.

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Insulinoma is a type of neuroendocrine tumour that constitutes 1—2 % of all pancreatic neoplasms [11]. It is the most common functional neuroendocrine tumour of the pancreas [14, 15]. The incidence is 1—4 people per million [14, 15, 19]. The first case was described in 1927 at the Mayo Clinic [19, 20]. Increased endogenous insulin secretion leads to hypoglycemia episodes [14, 15]. Insulinomas are commonly sporadic, but in 4—10 % they can be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome [11, 14, 20]. 90 % of sporadic insulinomas are solitary tumours compared with insulinomas in MEN1 syndrome that tend to develop earlier and be multifocal [11, 15, 20]. Besides that, 90 % of sporadic insulinomas are less than 2 cm in size and benign [15, 20]. The majority of

insulinomas are intrapancreatic, with approximately 2 % extra pancreatic localization, most commonly in the duodenal wall [14, 15].

Low glucose levels cause neuroglycopenic and autonomic adrenergic symptoms [11, 14, 15, 20]. Most noticeable are neuroglycopenic symptoms that present as blurry vision, diplopia, confusion, behavioural and personality changes, difficulty awakening and even seizures, loss of consciousness, or coma. The symptoms of the sympathetic nervous system are palpitations, diaphoresis, anxiety, tremor, nausea, and warmth sensations [11, 15, 20]. It can also result in weight gain as a result of more frequent meals to avoid fasting hypoglycemia-related symptoms [20]. Typically, hypoglycemia occurs during the fasting period or after exercise, although it can also be postprandial or have no relationship with eating [11, 14, 15, 20]. Historically, the diagnosis of insulinoma was based on the presence of Whipple's triad: hypoglycemia (plasma glucose < 50 mg/dL), neuroglycopenic symptoms, and prompt relief of symptoms following the administration of glucose [14, 15]. The current diagnosis of insulinoma relies on the measurement of plasma glucose, insulin, C-peptide, and proinsulin levels during a 72-hour fasting test, which should identify up to 99 % of insulinomas [15]. The C-peptide suppression test can also be used for screening or confirmation of insulinoma [14].

Surgery is the treatment of choice for insulinoma [13, 15, 16]. Other alternatives described can be endoscopic ultrasound (EUS)-guided alcohol ablation, radiofrequency ablation (RFA), or angioembolization [15]. Medical treatment with somatostatin analogues (octreotide or lanreotide and diazoxide) relies on symptom control [13, 16]. The type of surgical procedure — resection of the pancreas or enucleation, as well as an open or laparoscopic approach — depends on the location and size of the tumour; however, an individual approach is recommended [13]. For tumours > 2 cm in size, pancreatic resection is considered; for lesions < 2 cm, enucleation is advised if the tumour is distant from the main pancreatic duct [5, 16]. In rare cases with large insulinomas of the pancreatic head or tumours located close to the main pancreatic duct, pancreatoduodenectomy with or without pylorus preservation may be indicated [13]. For precise localization of the tumour and planning of the extent of surgery, computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor PET scans, or EUS are recommended [13, 15, 16]. EUS is more optimal for small lesion detection with 86 % sensitivity and 92 % specificity and allows for needle aspiration or core biopsy [16]. Intraoperative ultrasonography (IOUS) eases lesion localization in the pancreas and liver and is mandatory before pancreatic resection in MEN1 syndrome patients [16].

Follow-up should include regular assessment of clinical symptoms, biochemical analysis, and conventional or somatostatin receptor-sensitive imaging. For patients with R0/R1-resected neuroendocrine tumours (NET) G1-G2, control imaging with CT or MRI is recommended every 3—6 months. For patients with NET G3 or advanced disease, every 2—3 months. The follow-up period should be lifelong, while the control imaging intervals for staging may be extended to 1—2 years with an increasing length of follow-up [16].

Case presentation

A 29-year-old woman is seeking medical attention due to nonspecific complaints of recurrent episodes of dry cough and the sensation of a lump in the throat for the last 2 years. Her past medical history is remarkable for episodes of generalized tonic-clonic seizure attacks dating back to the age of 17, but possible hypoglycemic episodes were never documented. At that time, she was consulted by a neurologist; an MRI of the head revealed no pathology, and she was prescribed Lamotrigine 25mg twice a day for epilepsy. She had seizure attacks approximately once every 6 months; the last known seizure episode was 2 years ago. She had an outpatient visit to the gastroenterologist and pulmonologist, and proton pump inhibitor and glucocorticoid inhalation therapy were prescribed, leading to no improvement in complaints. In November 2021, she underwent a fibrogastroduodenoscopy and a fibrocolonoscopy, but without any pathological findings. In the same month, she had been assigned by her general practitioner to an abdominal MRI, where, incidentally, neoplasia of the pancreatic tail, measuring 1.1 cm in diameter, was discovered. A neuroendocrine tumour was suspected (Fig. 1). With suspicion of insulinoma and hypoglycemic episodes as possible causes of seizure attacks in the past, the patient was admitted for further investigations at the Department of Endocrinology. She has no other relevant medical or surgical records. The first time hypoglycemia (2.99 mmol/L) was officially documented was in 2019. She underwent a 72-hour fasting test and had hypoglycemia of 2.39 mmol/L with an unsuppressed C-peptide level of 0.77 ng/mL, which confirmed a diagnosis of insulinoma. A neurologist and an otorhinolaryngologist both consulted with the patient. MEN1 syndrome was excluded by performing screening for elevated thyroid, parathyroid, and adrenal gland hormones, which were in a normal reference range, and by the absence of any other radiological findings or relevant symptoms.

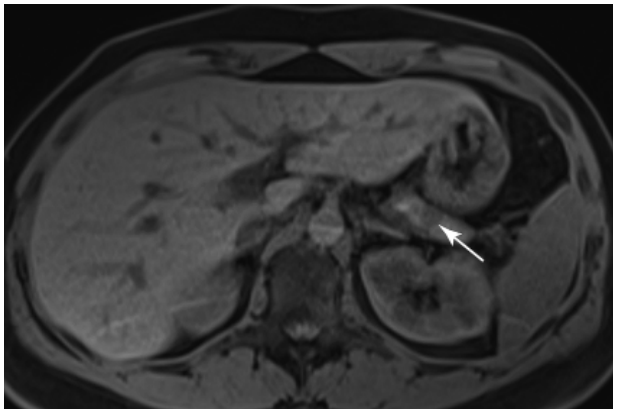

Figure 1. **MRI of the abdomen, T1 pre contrast phase.** Arrow — neoplasm of the pancreatic tail

Investigations

Tumour markers	
CA19-9	7.54 U/mL
NSE	11.9 ng/mL
72-hour fasting test	
Glucose	2.39 mmol/L
C-peptide	0.77 ng/mL
Adrenocorticotropic hormone	11.3 pg/mL
Cortisol	9.9 μg/dL
Biochemical analysis	
Thyrotrophic hormone	1.0500 μIU/mL
Parathyroid hormone	43.86 pg/mL
Cortisol	8.2 μg/dL
HbA1c	5.16 %
Random blood glucose	4.45 mmol/L
Ca	2.49 mmol/L
Testosterone	0.273 ng/mL
Sex hormone binding globulin	19.48 nmol/L
Free androgen index	4.86 %

Differential Diagnosis

It is important to differentiate between functional and nonfunctional pancreatic neuroendocrine neoplasms (pNEN). Functional pNENs cause clinical symptoms due to increased hormonal secretion. Table 1 lists the most common functional pNENs, their specific hormones, which are used for confirmation of diagnosis, and incidence rates [10, 14]. Nonfunctional pNENs constitute 70—90 % of pancreatic tumours and do not cause any specific clinical symptoms [14, 16]. Nonfunctional pNENs are generally diagnosed at more advanced stages because of the delay in the onset of symptoms, although their number is currently increasing due to incidental radiological findings [4].

Treatment

During a multidisciplinary team discussion, the decision was made to perform laparoscopic insulinoma enucleation. In January 2021, the patient underwent laparoscopic spleen-preserving distal pancreatectomy. After mobilization of the gastrocolic ligament and opening of the lesser sac, an inspection of the pancreas was performed. As a result, an approximately 6mm lesion in the upper anterior side of the pancreatic tail was discovered and enucleated. However, previously described in magnetic resonance, insulinoma was bigger in size and located more towards the posterior aspect of the pancreas and more towards the pancreatic tail. Therefore, the decision was made to perform IOUS for an additional assessment of pancreatic parenchyma. IOUS revealed another lesion deep in the parenchyma of the pancreatic tail that was not suitable for enucleation. The decision to perform distal pancreatectomy with spleen preservation was made. The overall time of operation, including intraoperative ultrasonography, was 1 hour 45 minutes.

Table 1. **Functional pancreatic NEN**

Type of neoplasia	Specific hormone	Incidence
Insulinoma	Insulin	1—4 per million
Gastrinoma (Zollinger-Ellison syndrome)	Gastrin	0.5—4.0 per million
VIPoma (Verner-Morrison syndrome)	Vasoactive intestinal polypeptide (VIP)	0.05—0.2 per million
Glucagonoma	Glucagon	1 per 20 million
Somatostatinoma	Somatostatin	0.025 per million
ACTHoma	Adrenocorticotropic hormone	Approx. 150 cases
Serotoninoma	Serotonin	Approx. 40 cases

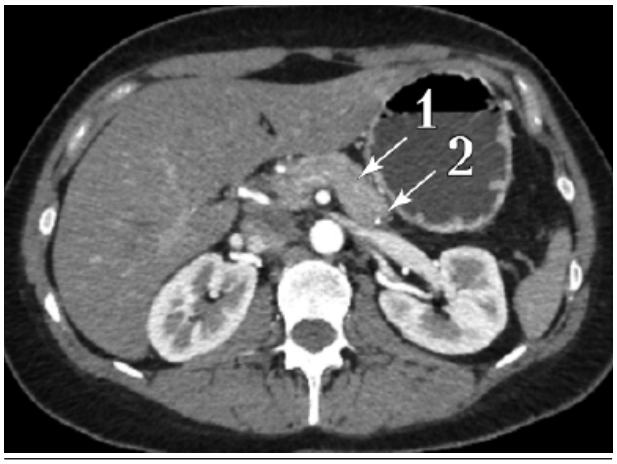

Figure 2. **Control CT scan of the abdomen, arterial phase. 4 months after operation. No evidence of recurrence or postoperative complications.** 1 — pancreas; 2 — resection line

Table 2. **Case reports with multifocal insulinomas**

Publication	Number of insulinomas	Association with MEN1
B. Babic et al, 2016	4	No
T. I. Gamboa-Jiménez et al, 2018	5	Yes
A. Tartaglia et al, 2022	3 + insulinomatosis	No
J. R. Snaith et al, 2020	3 + insulinomatosis	No
E. Borazan et al, 2015	5	No

Outcome and follow-up

The postoperative course was uneventful, and the patient was discharged on the 7th day after surgery. Two samples, 0.5 cm and 1.0 cm in size, were sent for pathology. Both samples showed an insulinoma with a TNM stage of pT1N0M0 P-N-R0, Grade 1, Ki-67 % < 2 %, I stage. Follow-up was done four months after discharge from the hospital. The control CT scan of the abdomen did not show any sign of recurrence of disease, pancreatic pseudocysts, or other postoperative complications (Fig. 2). Following the operation, the patient did not have any hypoglycemic or seizure episodes. She completely returned to her daily activities and work.

Discussion

The overall incidence of insulinomas is known as 1—4 per million. In the latest studies, the incidence rate remains the same. In 2021, a Kayo Ikeda Kurakawa et al. study in Japan for 2010—2018 showed an incidence of 3.27 per million [9]. In the 2022 E. Svensson et al. study in Japan for 2002—2019, the incidence was 1.3 per million [22]. Multiple insulinomas constitute less than 10 % of all insulinomas [2, 3]. Table 2 lists similar case reports of multifocal insulinomas described by other authors [1, 2, 6, 21, 23]. In some of the cases, insulinomatosis was described as multifocal benign insulinomas without MEN1 syndrome, which histologically is recognized by insulin-expressing monohormonal endocrine cell clusters (IMECCs) [21].

So far, our patient has not shown any signs of recurrence. Based on the Mayo Clinic study, the recurrence rate for patients without MEN1 syndrome is 5 % at 10 years, compared with 21 % at 10 years for patients with MEN1 [19—21]. There is limited information about late follow-up data on recurrence. In the same Mayo Clinic study, recurrence after 20 years was 7 % without MEN1 and 21 % with MEN1 [19]. In 2021, E. Peltola et al. presented long-term mortality and morbidity results in Finland for a period of 1980—2010. Median follow-up after diagnosis of insulinoma was 10.7 years. The overall survival rate for non-metastatic insulinoma was not different from the general population. The 10-year and 15-year disease-free survival rates were 93 % and 90 %, respectively. For metastatic insulinomas, 10-year survival was 33 % [17]. During follow-up, they found an increased incidence of cardiovascular disease, especially atrial fibrillation, in patients with insulinomas compared with the control group [17]. E. Borazan et al. (2015) described no recurrence 18 months after surgery for patients with multifocal insulinomas [2]. In 2020, J. R. Snaith et al. described a case of a patient who had two recurrences of insulinomas and hyperinsulinemic hypoglycemia episodes during a 9-year period. The patient twice had insulinoma resection, but hypoglycemia reoccurred. 2 years after the last resection, the patient underwent a total pancreatectomy, and histologically, insulinomatosis was confirmed, but in 6 weeks, hypoglycemia reoccurred again [21].

As mentioned before, surgery is the treatment of choice for insulinomas, with cure rates ranging from 77 % to 100 % [12, 20]. The operation can be done with an open or laparoscopic approach, and it also depends on the surgeon's experience in pancreatic surgery. In a 2021 study from Japan covering the 2010—2018 period, the laparoscopic approach was used at 29.2 % [9]. The extent of operation — resection or enucleation — relies on location, size, and relation to the Wirsung duct [12, 20]. Based on the ESMO 2020 guidelines, pancreatic resection is recommended for tumours larger than 2 cm in size, while

enucleation is advised for lesions smaller than 2cm if the tumour is at least 2—3 mm away from the main pancreatic duct to prevent the formation of a fistula [5, 16]. Therefore, a more preferred method is enucleation, which is the pancreas spearing technique, due to the fact that 90 % of insulinomas are solitary and < 2 cm in size [20]. For lesions < 1 cm in size, preoperative and intraoperative localization might be difficult. For better intraoperative localization of lesions, bimanual palpation together with IOUS is advised [2]. Palpation alone has 70 % sensitivity, but together with IOUS, it reaches 85—95 % [3]. The publication by A. Mathur et al. mentioned an IOUS sensitivity of 86 % [11]. In a study by C. L. Roland et al., the 96.7 % sensitivity of IOUS was compared with 63.9 % in preoperative CT scans [18].

This case clearly shows the advantages of IOUS-guided surgery in achieving better visualization and outcomes. After enucleation of the smaller lesion without the use of IOUS, other insulinomas would be missed and left in place because they were located deeply in the parenchyma. Simple visualization and palpation would not be enough. The use of IOUS is also recommended in the ESMO 2020 guidelines [16]. E. Borazan et al. presented a case similar to this in 2015 in which they operated on a 20-year-old patient who had two locations of insulinoma found preoperatively using CT and EUS. With the use of IOUS, they found three additional localizations of insulinoma that were not detected previously [2]. It is important to emphasize that sometimes it is possible to encounter multifocal locations of tumours, and intraoperative visualization and palpation, together with preoperative radiological findings, may be insufficient for the removal of all localizations and the provision of curative treatment. The use of IOUS can also help to determine the proximity of lesions to the pancreatic duct and help to decide whether resection or enucleation should be performed. Based on the previous facts, IOUS should be included in routine use during insulinoma operations.

The wide spectrum of symptoms, which are not exclusively specific to hypoglycemia and insulinomas, can make it difficult to establish the correct diagnosis and can be mistaken for other psychiatric or neurologic disorders [15, 20]. The average duration from the onset of symptoms until diagnosis can range from several months to more than several decades [20, 22]. Nowadays, with the improvement of diagnostics, this period shortens. Currently, no data is available on the duration from the onset of symptoms until diagnosis between different age groups. In the E. Peltola et al. Finland study, the mean age of diagnosis was 51.7 and the median duration of symptoms until diagnosis was 13 months [17]. In the E. Svensson et al. Sweden study for a period of 2002—2019, the mean age at diagnosis was 56, and the mean duration from the onset of symptoms until diagnosis was 7 months. In 3 of 41 cases, those patients were falsely diagnosed with epilepsy [22]. Kayo Ikeda Kurakawa et al. described a younger age of diagnosis in patients with malignant insulinoma compared with the benign group (55.5 vs. 66.0 years, $p < 0.001$). There was no difference in distribution between genders, although insulinoma was more prevalent among female patients in the benign group (65.3 % vs. 55.9 %, $p = 0.061$) [9]. P. R. Nashidengo et al. have described a similar case of a 26-year-old patient who had been previously diagnosed with epilepsy and schizophrenia due to a 3-year history of recurrent episodes of confusion, seizures, aggressive behaviour, polyphagia with weight gain, and loss of consciousness. During another episode of loss of consciousness, the patient was admitted to the hospital, and hypoglycemia was discovered. After additional investigations, an insulinoma of the pancreas was found, and enucleation of the tumour was done. Following the operation, the patient no longer experienced fatiguability, periods of increased appetite, seizures, or loss of consciousness and no longer used medications to control epilepsy and schizophrenia [12].

There are a few similar case reports with patients who had hyperinsulinemic hypoglycemia episodes with seizures. Most likely, previous epileptic episodes in our patient were manifestations of non-recognized hypoglycemic episodes. However, it is hard to prove because the patient did not have any new epileptic episodes for the last 2 years. In 2021, C. Inoue et al. published a case of a 28-year-old patient who had had severe congenital hyperinsulinemic hypoglycemia dating back to the age of 6 months with developmental disorders and epilepsy. The patient was treated medically with diazoxide and antiepileptics for 28 years until they developed acute necrotizing pancreatitis, assumed to be drug-induced due to diazoxide. After additional investigations, diffuse hypersecretion of insulin from the whole pancreas was found, and the patient had a subtotal distal pancreatectomy with splenectomy. Histologically, microinsulinomatosis with lymph node metastases was diagnosed [7]. M. A.R. Khan et al. described another case of a 22-year-old patient who had been complaining of increased hunger, tremors, perspiration, palpitations, confusion, and frequent seizures for the previous three years. In a CT scan, an insulinoma in the neck of the pancreas was found, and the patient underwent Whipple's procedure — pancreaticoduodenectomy [8].

Patient's perspective

Overall, the patient's perspective is good. Operative treatment can provide a cure in 77—100 % of cases [12, 20]. In a case of benign insulinoma without MEN1, the 10-year and 20-year recurrence risks are 5 % and 7 %, respectively. The last follow-up did not show any signs of pancreatic insufficiency or other postoperative complications. The patient can get back to her usual daily activities with no performance restrictions.

Learning points/take home messages

Multifocal insulinomas are rare, usually benign, functional pancreatic neoplasms that can be cured with surgery. A minimally invasive laparoscopic approach with elective IOUS can improve surgical outcomes and the patient's quality of life.

Declaration of interests

The disclosed information is correct and no apparent conflict of interest is known. Authors have no fundings, business or financial interest in current work.

Ethics approval and written informed consents statements

Clinical case report is approved by the Ethics committee of Riga East Clinical University Hospital. Patient has given consent for publication of clinical case report and has been introduced with publication content.

Authors contributions

E. Bobrovs: clinical case report, review literature of similar publications; J. Pavulans, H. Plaudis: supervision of the creation of publication and edition of the content; I. Konrade: consultations on the aspects of endocrinology and diagnostics; R. Laguns: help in selection of proper images from radiological investigations.

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Пацієнт з мультифокальною інсуліномою підшлункової залози: рідкісний випадок функціонального нейроендокринного новоутворення підшлункової залози

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Інсулінома — це тип нейроендокринної пухлини з частотою 1—4 випадки на мільйон. Множинні інсуліноми становлять менше 10 % від усіх інсуліном. Методом вибору інсуліном є оперативне видалення пухлини. Хірургічне втручання може бути виконане відкритим або лапароскопічним доступом та має показники виліковності від 77 до 100 %. При пухлинах розміром понад 2 см пропонується резекція підшлункової залози, тоді як при ураженнях менше 2 см — енуклеація якщо пухлина знаходиться на відстані не менше 2—3 мм від головної панкреатичної протоки для запобігання утворенню нориці. Для кращої інтраопераційної локалізації уражень рекомендується бімануальна пальпація разом з інтраопераційним ультразвуковим дослідженням (ІОУЗД). Чутливість лише пальпації становить 70 %, але в поєднанні з ІОУЗД вона досягає 85—95 %.

Молода пацієнтка 20 років була обстежена з неспецифічними скаргами та історією хвороби на епілепсію з 17-річного віку. Аналіз крові виявив тяжку гіпоглікемію, а магнітно-резонансна томографія виявила новоутворення в тілі підшлункової залози розміром 11 мм. За допомогою 72-годинного тесту натщесерце діагноз інсуліноми було підтверджено, і пацієнтці виконали лапароскопічну операцію. Для точної локалізації ураження було проведено ІОУЗД, під час якої було виявлено додаткову пухлину в хвості підшлункової залози. Виконано лапароскопічну дистальну панкреатектомію зі збереженням селезінки. Гістологічне дослідження підтвердило мультифокальну інсуліному 1 ступеня. Післяопераційний перебіг був без ускладнень. Через 4 міс було виконано контрольну комп'ютерну томографію, на якій не було виявлено ознак рецидиву інсуліноми, псевдокіст підшлункової залози або інших ознак післяопераційних ускладнень. Після операції у пацієнтки не було жодних епізодів гіпоглікемії чи судомних нападів.

Широкий спектр симптомів, які не є специфічними для інсуліноми, зокрема епілепсія, може ускладнити постановку правильного діагнозу і помилково прийнятий за інші психіатричні або неврологічні розлади. Даний випадок наочно демонструє доцільність хірургічного втручання під контролем ІОУЗД у досягненні кращої візуалізації та результатів. Після енуклеації меншого вогнища без використання ІОУЗД інша інсулінома була б пропущена і залишена на місці, оскільки розташовувалась глибоко в паренхімі і не пальпувалася.

Ключові слова: мультифокальна інсулінома, хірургічне лікування, інтраопераційне ультразвукове дослідження, напади.

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