CASE REPORTS

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Pathological aspects underlying pancreatogenous hyperinsulinemic hypoglycemia – report of three cases

BOGDAN MIRCEA MIHAI[1)], CRISTINA MIHAELA LĂCĂTUŞU[1)], LIDIA IULIANA ARHIRE[1)], MARIANA GRAUR[1)], VIOREL SCRIPCARIU[2)], MARIA GABRIELA ANIŢEI[2)], IULIAN RADU[2)], DAN FERARIU[3)], MIHAI DANCIU[4)]

[1)]*First Medical Department – Diabetes, Nutrition and Metabolic Diseases, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy, Romania*

[2)]*Department of Surgery – Surgical Semiology and General Surgery, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy, Romania*

[3)]*Department of Pathology, Regional Institute of Oncology, Iassy, Romania*

[4)]*Department of Morpho-Functional Sciences – Pathology, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy, Romania*

Abstract

Pancreatogenous hyperinsulinemic hypoglycemia (PHH) is a rare disorder determined by an abnormally high secretion of insulin in the pancreas, in the absence of other medical or pharmacological factors. Either β-cell tumors (insulinomas) or β-cell hyperplasia (nesidioblastosis) can determine this pathology. Most publications on insulinomas or nesidioblastosis approached these subjects from a clinical point of view. This paper aims to analyze pathological aspects underlying pancreatogenous hyperinsulinemic hypoglycemia. We present two cases of insulinomas with unusual pancreatic localization and size, one of them showing amyloid deposits in the stroma. In both cases, immunohistochemistry confirmed the clinical and imagistic supposition. The third reported case refers to a 57-year-old patient with nesidioblastosis with isolated disposition of endocrine cells and areas of focal organization, both morphological aspects being extremely rare in adults. Although clinical and laboratory data are usually identical in the two forms of PHH, histopathological and immunohistochemical diagnosis is essential in differentiating insulinomas from nesidioblastosis, as the surgical management is different: enucleation for insulinomas and total or subtotal pancreatectomy for nesidioblastosis.

Keywords: pancreatogenous hyperinsulinemic hypoglycemia, insulinoma, neuroendocrine tumors, nesidioblastosis.

Introduction

Pancreatogenous hyperinsulinemic hypoglycemia (PHH) is a relatively rare pathology induced by an abnormal insulin secretion in the pancreas, in the absence of any concurrent disease or any medication that would induce insulin release from the β-cells. Clinical manifestations of PHH are included into the so-called Whipple's triad: signs and symptoms of hypoglycemia, glycemic levels less than 50 mg/dL and the prompt relief of symptoms after ingestion of carbohydrates or intravenous administration of glucose solutions [1]. Pathological anomalies underlying PHH are represented by proliferation of β-cell under the form of tumors (insulinomas) or diffuse or focal islet cell hyperplasia (nesidioblastosis).

Insulinomas are pancreatic endocrine tumors characterized by an abnormally high secretion of insulin leading to hypoglycemia [2]. Their incidence is estimated to one to three cases per million per year [3] and they account as the most frequent type of functioning pancreatic neuroendocrine tumors (up to 70% of cases) [3, 4]. Ectopic neuroendocrine tumors that secrete insulin and induce hypoglycemia are rare and have been reported in the duodenum, ileum, lung, cervix or ovary [4]. The highest incidence of insulinomas occurs in the fifth decade of life [3, 4]. Most insulinomas (85% to 99%) are small (diameters less than 2.5 cm) and solitary [5]. A reduced proportion of patients (2% to 10%) have multiple insulinomas, with synchronous or metachronous manifestations [3, 4]. The diagnosis is based on clinical, laboratory and imagistic data, and confirmed by histopathology and immunohistochemistry tests.

The other form of PHH, with no identification of insulinomas, is represented by nesidioblastosis. Although utilized by some authors to designate any proliferation of endocrine cells from the ductal epithelium of the pancreas [6], the term "nesidioblastosis" is frequently used for cases of non-tumorous β-cells proliferation leading to persistent hyperinsulinemic hypoglycemia of infancy or non-insulinoma PHH in adults [7]. The definition of pancreatic endocrine cells hyperplasia is still subject to controversies; some authors describe it as the expansion of the endocrine cells mass to more than 2% of the total pancreatic mass in adults or more than 10% in infants, while others use criteria such as islets diameters over 250 μm and an increased number of islets [8, 9]. Nesidioblastosis is usually seen in infants and is very rare in adults.

We present two cases of insulinoma and one case of nesidioblastosis leading to PHH, with highlight on their pathological aspects. We also refer to the most recent pathological criteria for diagnosis and their application on clinical practice.

Case reports

Case No. 1

An 18-year-old female was addressed to the Clinic of Diabetes, Nutrition and Metabolic Diseases for adrenergic

and neuroglycopenic symptoms of hypoglycemia (sweating, dizziness, sleepiness) in the last 13–14 months. Symptoms appeared after nocturnal fasting and resolved after ingestion of carbohydrates. Before admission in our clinic, she had already been explored by craniocerebral computed tomography (CT) and magnetic resonance imaging (MRI), both without any abnormal result. One month before addressing to our service, a low glycemic value (17.7 mg/dL, reference values 70–110 mg/dL) was detected in fasting conditions during a symptomatic episode. After admission into our clinic, frequent oligosymptomatic hypoglycemic episodes down to 32 mg/dL recurred during night, early morning and late postprandial periods, corresponding to high insulinemic values between 54.7 and 110 μIU/mL (reference values 5–28.4 μIU/mL). There was no history of chronic illnesses or medications and her physical examination was unremarkable. No tumoral images were present on chest X-ray or abdominal ultrasonography. Abdominal angio-CT detected a 1.5 cm nodule in the cephalic pancreas, with intense, predominantly peripheral, contrast capture in arterial time and isodense in venous time. The other endocrine-related and genetic testing excluded the presence of a multiple endocrine neoplasia type 1 (MEN-1). She was referred to the surgery department, where enucleation of the pancreatic nodule was performed; temporary hyperglycemia appeared in the immediate postoperative period, but at the time of discharge glycemic values normalized. She experienced no other hypoglycemic episodes afterwards.

At gross examination, the resected specimen was represented by an ovoid soft nodule, measuring 2.2/1.5/1.2 cm and weighing 1.682 g. The external surface was smooth, vaguely bosselated. On cut surface, the nodule was red.

Histologically, the tumor was represented by an epithelial proliferation, with diffuse or trabecular architecture, and isolated rosettes (Figure 1). Tumor cells were polyhedral, with large, round nuclei, dispersed chromatin, 1–2 nucleoli, and abundant, eosinophilic, granular cytoplasm. Some cells presented intracytoplasmic eosinophilic inclusions. Mitotic activity was low (3 mitoses/2 mm^2). Stroma was reduced, with vessels.

Immunohistochemistry revealed intense and diffuse positivity for chromogranin (Figure 2) and synaptophysin (Figure 3) of tumor cells. CD56 was diffusely positive in tumor cells. Ki67 was positive in 5% of the tumor cells, evaluated in the mitotically most active areas.

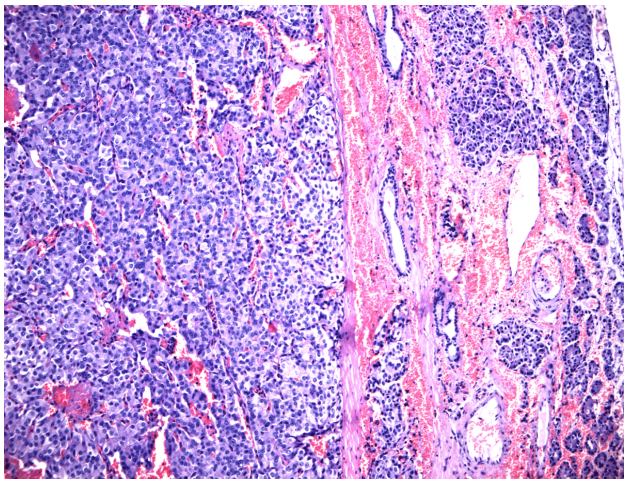

Figure 1 – ***Insulinoma (left) with prominent trabecular architecture and rosettes (focally); normal pancreatic tissue (right) (HE staining, ×100).***

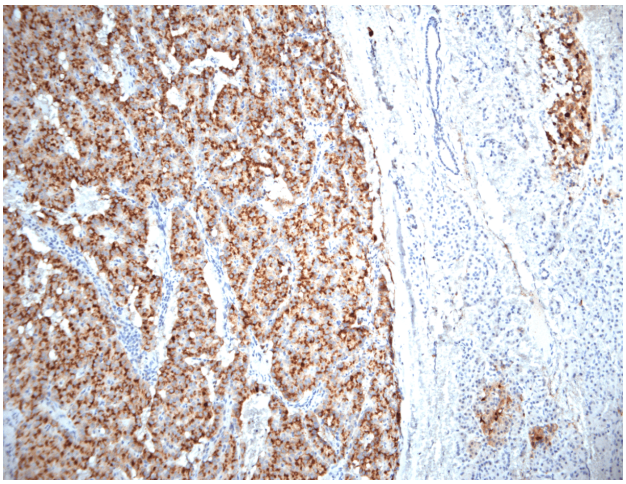

Figure 2 – ***Insulinoma (left): chromogranin A intense positive in tumor cells and in pancreatic endocrine islets (Antibodies anti-chromogranin A, ×100).***

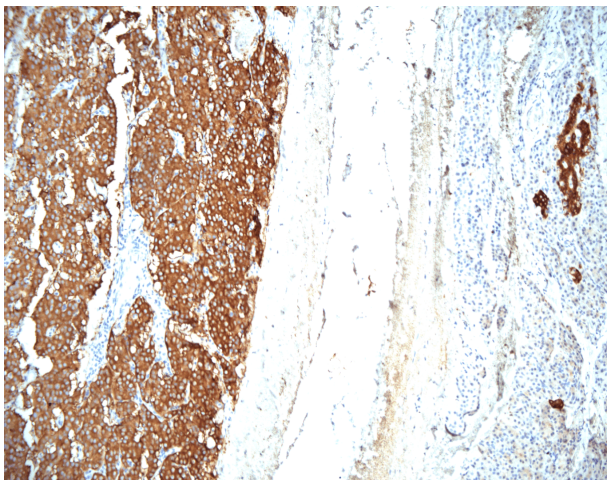

Figure 3 – ***Insulinoma (left): synaptophysin intense positive in tumor cells and in pancreatic endocrine islets (Antibodies anti-synaptophysin, ×100).***

Morphological aspects and immunohistochemical profile were consistent with the diagnosis of neuroendocrine tumor (NET G2), pancreatic insulinoma in the clinical context.

Case No. 2

A 43-year-old female was admitted in our clinic for confusion, blurred vision and slow thinking installed for approximately one year in nocturnal or otherwise prolonged fasting conditions. Symptomatic episodes resolved after eating foods with high or medium glycemic index. In the first 24 hours after admission, frequent hypoglycemic episodes (59 to 43 mg/dL) with minimal symptomatology occurred, with high fasting and postprandial levels of insulinemia (55.2 and 131 μIU/mL, respectively). Her medical history was limited to hypothyroidism and her only chronic treatment was thyroid hormones replacement. The repeated endocrine controls revealed no other pathology suggestive for the existence of a MEN-1.

Physical examination was essentially normal, except for a palpable mass in the pelvic region. Chest X-ray was normal and abdominopelvic ultrasonography detected a uterine tumor suggestive for a fibroma, but no pathological images at pancreatic level. Abdominal CT showed no evidence of a pancreatic nodule, but abdominopelvic MRI, besides confirming the uterine fibroma-like tumor, detected a 1.2/1.5 nodule at the limit between the pancreatic head and the uncinated process. The patient was addressed to surgery, where interanexial subtotal hysterectomy and resection of the pancreatic nodule were performed without incidents, except transitory hyperglycemia with spontaneous resolution a few days after intervention. The patient was discharged in good health and with normal glycemic levels, and no other hypoglycemic episode recurred after surgery.

The uterus surgically resected during subtotal hysterectomy measured 15/13.5/11.5 cm (the uterine corpus) and 1.5 cm (the isthmus). On cut surface, the virtual uterine cavity (5.5 cm length) was delineated by a thin endometrium. In the myometrium, we noticed a large (14/13/11 cm), well-circumscribed, white-ivory nodule of elastic consistency and whorled appearance. The pancreatic resection sample of 2.5/2/1.5 cm in size contained a well-delineated, white-yellowish, firm nodule (1.7/1.7/1.3 cm and 1.571 g).

Histology of the uterine tumor was typical for leiomyoma, while the microscopic examination of the pancreatic nodule revealed a pancreatic neuroendocrine tumor – G2, with solid or trabecular architecture (Figure 4). No areas of tumor necrosis were identified. Mitotic count found 2 mitoses/10 high-power fields (HPF). Small amounts of amyloid were identified in interstitium, confirmed by Congo Red staining and apple green birefringence under polarized light.

Immunohistochemistry revealed CD34 positive in vessels, cytokeratin 34betaE12 focally positive in tumor cells and CD56 intensely diffuse positive in tumor cells (Figure 5). Chromogranin was positive, but with uneven distribution in the tumor cells and synaptophysin was diffusely positive in tumor cells (Figure 6). Ki67 was positive in more than 3% of tumor cells, evaluated in the mitotically most active areas.

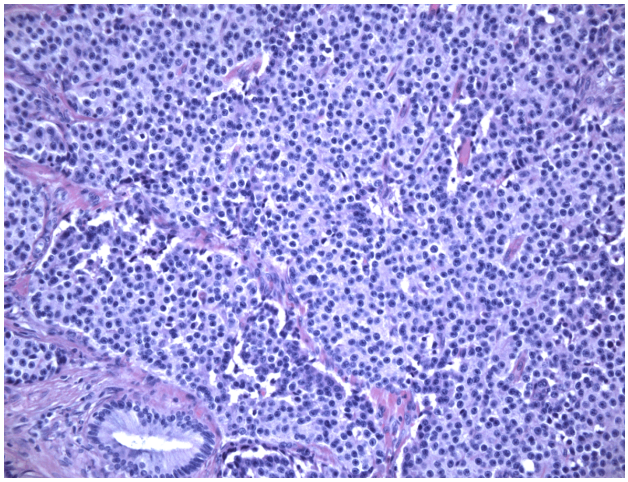

Figure 4 – ***Insulinoma with solid architecture and rosettes (focally) (HE staining, ×200).***

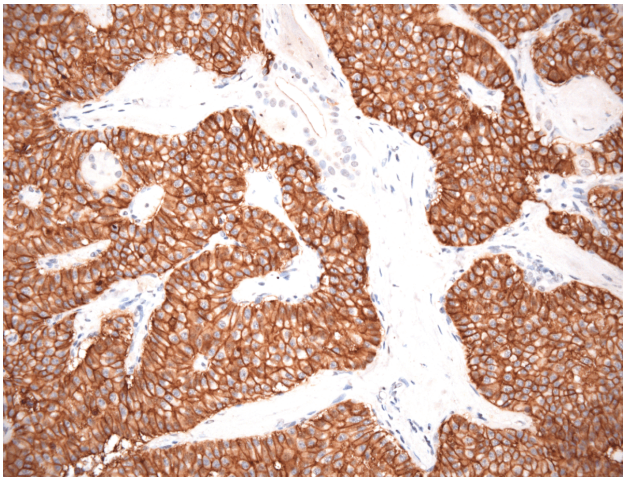

Figure 5 – ***Insulinoma: CD56 intense positive in tumor cells' membranes (Antibodies anti-CD56, ×200).***

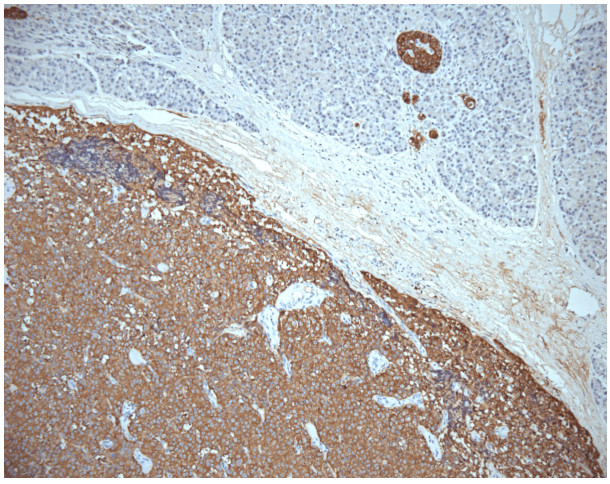

Figure 6 – ***Insulinoma (lower-left): synaptophysin intense positive in tumor cells and in pancreatic endocrine islets (Antibodies anti-synaptophysin, ×100).***

Morphological, immunohistochemical and clinical data were consistent with the diagnosis of neuroendocrine tumor (NET G2).

Case No. 3

A 57-year-old male was admitted in the emergency unit and afterwards in our clinic for episodes of confusion, loss of memory, lack of concentration and coordination appearing in the last month in both fasting and late postprandial conditions and responding to food intake. Glycemic levels determined in emergency unit were 34 mg/dL, resolving after intravenous administration of glucose solutions and eating. Hypoglycemic episodes down to 11 mg/dL reappeared rapidly after admission in our clinic, corresponding to high insulinemic values of 51.9 μIU/mL and high levels of C-peptide (14 ng/mL). His medical history was represented by right carotid artery stenosis, left renal artery thrombosis with secondary renovascular hypertension and aortobifemoral bypass for peripheral arterial disease. Chronic therapy consisted in Zofenoprilum, Isosorbide dinitrate, Nebivololum, Clopidogrelum, Sulodexidum, Pentoxiphyllinum and Rosuvastatinum. Clinical examination revealed no other physical signs except those related to the above-mentioned conditions. The endocrine-related laboratory data showed no abnormal values. Chest X-ray was normal;

abdominal ultrasonography and angio-CT showed a smaller right kidney, but no signs of pancreatic or intra-abdominal tumor. Abdominal MRI was not performed due to limited cooperation of the patient to the technical requirement of the procedure, while access through selective angiography was prohibited due to the presence of the aortobifemoral bypass. The patient then addressed to the surgical department, where intraoperative palpatory and ultrasonography exploration of the pancreatic mass were performed, where the only finding was a portion of the cephalic pancreas suggesting a nodular aspect at clinical inspection (without echographic confirmation). This fragment together with distal pancreas and spleen were resected. In the first weeks after surgery glycemic levels got back to normal, but afterwards hypoglycemic episodes reoccurred and presently the patient is considering subtotal pancreatectomy, as Diazoxide treatment is not available in our country.

Three surgically resection specimens were addressed to the pathology department. The first one, after corporeo-caudal pancreatectomy (11.5 cm length) including the spleen (10/8/6 cm), was represented by pancreatic tissue with lobular aspect on cut surface. Neither the pancreas, nor the spleen presented changes at gross examination. The other two specimens were represented by a 1.9/1.5 cm pancreatic nodule and a 1.5 cm diameter nodule adjacent to the inferior border of the pancreas.

Microscopic examination of the first two samples revealed pancreatic parenchyma with numerous neuro-endocrine type cells, isolated or describing islets or nests, irregularly distributed into the intra- or interlobular spaces. Ductulo-insular complexes, comprising endocrine islets in intimate association with small-sized ducts, were observed (Figure 7). The majority of these endocrine islets presented cells with hyperchromatic, enlarged nucleus, distinct macronucleolus and clear cytoplasm, yet no mitotic activity was identified. Adjacent exocrine pancreatic parenchyma preserved the normal, lobular architecture with normal sized ducts and uniformly distributed inclusions of endocrine islets. Sixteen lymph nodes (including two from the third surgical specimen) presented normal morphology, free of metastases.

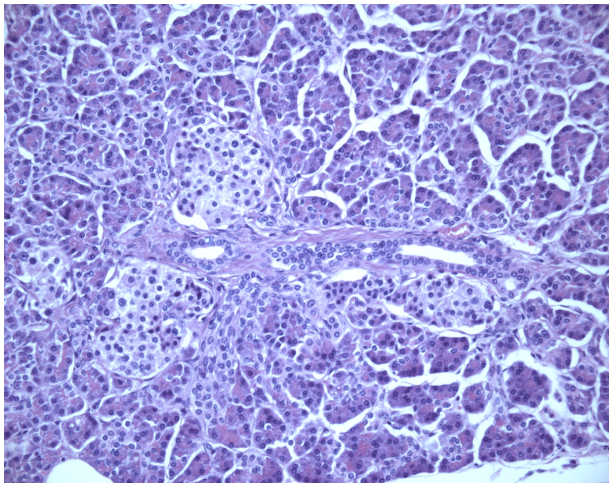

Figure 7 – ***Nesidioblastosis: pancreatic parenchyma with ductulo-insular complexes, comprising endocrine islets in intimate association with small-sized ducts (HE staining, ×200).***

Morphological aspects were consistent with the diagnosis of diffuse endocrine (islet) cell hyperplasia (nesidioblastosis).

Histopathological processing

In all the three cases, the resected specimens were sent to the pathology department. All the fresh resection specimens were weighed and measured, then fixed in 10% neutral buffered formalin and routinely processed by paraffin embedding. Five μm sections were stained using Hematoxylin–Eosin (HE) and van Gieson trichromic. Amyloid was proved using Congo Red staining, which revealed a dull brick red coloration for these deposits in direct light and an apple green birefringence in polarizing microscopy.

Immunohistochemistry was performed using the following monoclonal antibodies: anti-CD34 (clone QBEnd10, 1:50, Novocastra, Germany), anti-cytokeratin (1/5/10/14) (clone 34betaE12,1:100, Novocastra, Germany), monoclonal antibodies anti-CD56 (clone 1B6, RTU, Novocastra, Germany), anti-chromogranin A (clone 5H7, 1:250, Novocastra, Germany), anti-synaptophysin (clone 27G12, 1:250, Novocastra, Germany), anti-Ki67 (clone MM1, 1:50, Novocastra, Germany). For antigen retrieval, we used heat induced antigen retrieval (HIER) in pH 6.0 citrate buffer in a steamer. To visualize the reaction we used NovoLink™ Polymer Detection System (Leica Biosystems, Germany).

Each slide was independently evaluated by two pathologists.

Discussion

Insulinoma-induced PHH

Starting from the presentation of two cases of insulinomas, our paper aims to address this subject predominantly from the pathological perspective and to correlate it to the clinical approach already present in the literature.

The highest incidence of insulinomas is believed to be in the fifth decade of life [3, 4]. However, one of our patients was 18-year-old, proving that such tumors can be encountered over a much wider age range. Both our patients were females, similar to most cases presented in the literature, where incidence of insulinomas is considered slightly higher in females than in males [3]. In both our cases, patients were otherwise healthy individuals; this situation is similar to the general presentation of non-diabetic hypoglycemias, as it is widely accepted today that insulinomas are the most frequent cause of hypoglycemia in patients with no significant systemic illnesses where factitious hypoglycemia is excluded [1].

Tumor localization in both our cases was in the head of the pancreas, different from the usual localization of most insulinomas in the pancreatic tail [10]. Macroscopic aspect was different for the two cases; the first presented as an ovoid soft nodule of 1.682 g, with a smooth, vaguely bosselated external surface and reddish on cut surface; the second was a well-delineated, white-yellowish, firm nodule of 1.571 g.

Both cases of insulinomas that we presented were identified using imagistic techniques, thus facilitating curative surgical resection. This was possible in the context

of relatively large tumors in both cases (2.2/1.5/1.2 cm in the first case, 1.7/1.7/1.3 cm in the second case), compared to the small dimensions insulinomas are usually reported to have. According to previous data, 90% of insulinomas have diameters less than 2 cm, 50% less than 1.3 cm and 30% less than 1 cm [11]; this is perhaps the reason why existing literature mentions that only approximately two-thirds of the insulin-secreting tumors can be localized in the preoperative stage using the imagistic techniques [12].

The second case we presented had small amounts of amyloid in the interstitium, confirmed by Congo Red staining and apple green birefringence under polarized light. Amyloid is present in approximately 50% of insulinomas and it has been quoted in the case of giant tumors [13, 14], where it possibly contributes to their enlarged size, being excessively produced and processed from islet amyloid polypeptide, which is secreted along with insulin from the β-cells [15]. Both our cases had positivity for chromogranin A, diffuse in the first case and with uneven distribution in the second case; diffuse positivity for synaptophysin was recorded in both cases. These markers are generally present in neuroendocrine tumors and have a diffuse positivity in most situations [16, 17], which was not the situation of chromogranin A in our second case.

Nesidioblastosis-induced PHH

The term of "nesidioblastosis" was first coined in 1938 by George Laidlaw, coming from the Greek words "nesidion" (islands) and "blastos" (germ), in order to designate the pancreatic endocrine cells' neoformation or neodifferentiation in the ductal epithelium of the exocrine pancreas [7]. Its initial mentioning was in children with congenital hyperinsulinemic hypoglycemia. The rare cases reported in adults since 1975 (less than 100) are believed not to have inherited mutations at their basis, in contrast with those previously reported in children [18]. In adult cases appearing after bariatric surgery, some authors suggest a possible role for the increased secretion of β-cytotropic growth factors such as IGF-2, IGF-1 receptor α and TGF-β receptor 3, leading to β-cells hypertrophy [18]. Another evidence comes from experimental studies, where GLP-1 analogues tested for diabetes therapy induced β-cells proliferation in rodents [19, 20].

In patients with PHH accompanied by morphological changes of nesidioblastosis, there are however some authors who consider that it is not clear if hyperinsulinism is entirely attributable to the histological changes, since previous data cite a frequency of 36% for nesidioblastosis autopsy findings without clinical signs of hypoglycemia [21]. Other opinions sustain that the whole histopathological criteria used nowadays to define adult diffuse nesidioblastosis are unclear or even questionable [7, 22]. Some other authors are reluctant with using the term of "nesidioblastosis" anymore, as it literally refers to islet cells budding off from ducts, a histological finding considered today to be highly suggestive, but not mandatory for this diagnosis [23]. Finally, there is also the problem of the techniques used to examine the samples; as it is quite difficult to diagnose diffuse nesidioblastosis on frozen sections, which make the enlarged nuclei of the β-cells difficult to recognize, standard histologic evaluation is advisable [7, 22, 23]. In such situations, close collaborative relationships between medical clinicians, surgeons and pathologists are required. Once this condition is accomplished, some authors affirm that β-cells hypertrophy, one of the main features of nesidioblastosis, is in most cases recognizable on Hematoxylin and Eosin-stained sections.

In our patient, microscopic examination of the resection samples showed the presence of all major criteria accepted today for the diagnostic of nesidioblastosis [7, 23]: no evidence of an insulinoma, multiple endocrine cells with hyperchromatic, enlarged nucleus and clear cytoplasm, but without mitotic activity. Similar to other reports [7, 22], the lobular architecture of the exocrine pancreatic tissue was preserved and pancreatic ducts were normal sized in resection samples analyzed in our patient. The endocrine cells had an increased number and were found either isolated or grouped in islets or nests, with an irregular distribution in the intra- or interlobular spaces. To the best of our knowledge, previous reports of an isolated disposition of endocrine cells in PHH induced by nesidioblastosis do not exist in literature. Irregular islet distribution in the intra- or interlobular spaces is present only in isolated reports of adult nesidioblastosis [24]. Distinct macronucleoli and ductulo-insular complexes, including endocrine islets intimately associated with small-sized ducts, were also observed. Ductulo-insular complexes that were present in our case, although highly suggestive for the existence of nesidioblastosis, are considered a minor diagnostic criterion and are reported in some but not all cases [7, 18, 24]. Macronucleoli are another minor diagnostic criterion [7] that was present in our case. The normal morphology and the absence of metastases in all the 16 lymph nodes that were studied also helped for differential diagnostic, as to exclude the alternative of a malignant insulinoma. The 1.9/1.5 cm nodule resected from the cephalic pancreas, also having microscopic features of nesidioblastosis, might suggest a trend of focal organization in the pancreatic endocrine parenchyma, raising analogies to focal nesidioblastosis, which is however not usually reported in adults. Only one paper in the consulted literature suggests the possibility of a "mixed type" of adult nesidioblastosis, associating features of both diffuse and focal types [25]; this possibility needs further analysis in other cases in order to certify its existence.

Conclusions

Insulinomas and nesidioblastosis are two rare clinical entities that may underlie pancreatogenous hyperinsulinemic hypoglycemia, a condition induced by the abnormally high insulin secretion in the pancreas. All our three cases represent therefore interesting uncommon clinical situations. Histopathological and immunohistochemical diagnosis was essential in differentiating insulinomas from nesidioblastosis, leading to a different surgical management: enucleation for insulinomas and subtotal pancreatectomy for nesidioblastosis.

Conflict of interests

The authors have no conflict of interests to declare in relation to this article.

Author contribution

All authors have equally contributed in preparing this manuscript and thus share first authorship.

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Corresponding author

Cristina Mihaela Lăcătuşu, Lecturer, MD, PhD, Discipline of Diabetes, Nutrition and Metabolic Diseases, First Medical Department, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy; Clinic of Diabetes, Nutrition and Metabolic Diseases, "Sf. Spiridon" Clinical Emergency Hospital, 1 Independenţei Avenue, 700111 Iassy, Romania; Phone +40723–211 116, e-mail: cristina.lacatusu@umfiasi.ro, cmlacatusu@yahoo.co.uk

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