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A suspected insulinoma with the unexpected histopathological finding of a nesidioblastosis - A case report and literature review

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ABSTRACT

Introduction: Nesidioblastosis is a hyperplasia of the beta cells that causes persistent hyperinsulinemic hypoglycemia, unfortunately, it is difficult to diagnose through imaging studies.

Case presentation: A 68-year-old woman with palpitations, diaphoresis, dizziness and alterations in the level of consciousness that improve with food intake. Laboratories: glucose 35.0 mg/dl, insulin 12.5 mUI/ml, proinsulin 14.1 pmol/L and peptide C 2.55 ng/ml. Octreoscan reveals an abnormal epigastric uptake area and the tomography shows a focal hypervascular lesion in pancreatic body of 12x11 mm. A distal pancreatectomy was performed without palpating the tumor in transoperative period, and a diffuse nesidioblastosis was reported in the histopathological study. The patient persists with hypoglycemia and an additional pancreatic resection was performed, resecting 90% of the organ. Although an insulinoma was not located in the piece, an area surrounded by connective tissue was observed where islet hyperplasia was more accentuated.

Discussion: The pathophysiology of nesidioblastosis is unknown, its main differential diagnosis is insulinoma and this should be suspected when the tumor can not be identified. Most agree that a pancreatectomy that involves 60-80% of the total organ can control glucose levels with low risk of diabetes and pancreatic

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insufficiency.

Conclusion: The nesidioblastosis should be suspected when a hyperinsulinemic hypoglycemia is difficult to control and when a tumor can not be identified. The extension of the pancreatectomy should be individualized and if an insulinoma is not localized and a nesidioblastosis is suspected, an intraoperative histopathological examination with frozen section evaluation for the margins could determine the extent of pancreatectomy.

Keywords: Nesidioblastosis; Insulinoma; Pancreatic tumor; Pancreatic neuroendocrine tumor; Hyperinsulinemia; Hyperinsulinemic hypoglycemia

INTRODUCTION

In 1938 George F. Laidlaw described nesidioblastosis as a diffuse proliferation of the islet cells of Langerhans in infants [1,2,3,4,5,6,7,8,9]; the current definition specifies a congenital or acquired beta cell hyperplasia that causes a persistent hyperinsulinemic hypoglycemia [2]. Although it is predominant in infants, the first case reported in adults was in 1975 [6], since then, less than 100 cases have been reported [4,7,9] and it constitutes between 0.5% -5% of causes of hyperinsulinemic hypoglycemia in this population. [2,4,5,6,7,8,10,11,12,13].

The main differential diagnosis of nesidioblastosis is insulinoma [2] and unfortunately it is difficult to diagnose by imaging studies [8]. In Selective Arterial Calcium Stimulation With Hepatic Venous Sampling (SACST), nesidioblastosis presents an increase in insulin levels after stimulation in several arteries [8,14]. Currently, this procedure is considered the best choice for the location of an insulinoma not visualized by tomography or endoscopic ultrasound [9], however, it should be taken into account that it is an invasive procedure and not free of complications [13].

Surgery is the treatment of choice, however the extent of resection is not well established [3] and the most frequent complications of pancreatectomy include insulin-dependent diabetes and recurrent hypoglycemia [6]. Some patients not suitable for major surgery require pharmacological management as well as those who persist with hypoglycemia after surgery.

CASE PRESENTATION

Female of 68 years old without chronic degenerative diseases with palpitations, diaphoresis, pallor, dizziness and alterations of the level of consciousness that predominate at early morning. This symptomatology improved with the intake of sweet food. In presence of a serum glucose of 35.0 mg/dl, insulin of 12.5 mUI/ml, proinsulin 14.1 pmol/L and peptide C 2.55 ng/ml are reported. After receiving medical treatment, the patient persists with symptomatic hypoglycemia. An octreoscan revealed an abnormal well-circumscribed uptake in the epigastrium below the left hepatic lobe suggestive of neuroendocrine tumor (**Figure 1**) and a hypervascular lesion in the arterial phase in the pancreatic body of 12x11 mm (**Figures 2 and 3**).

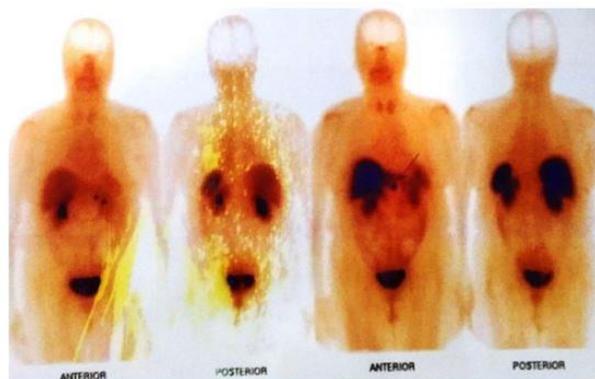
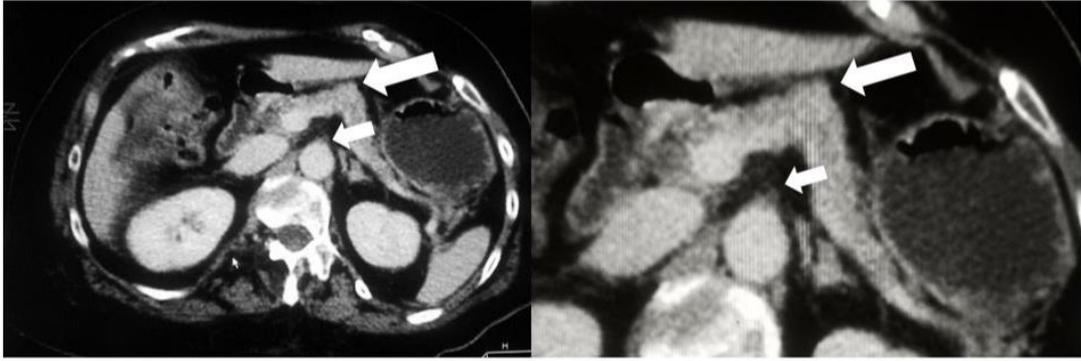


Figure 1. Octreoscan: A well circumscribed abnormal uptake zone anterior to the lower border of the left hepatic lobe.



Figures 2 and 3. Long arrows: Hypervascular focal lesion in arterial phase in pancreatic body of 12x11 mm. Short arrows: Emergency site of superior mesenteric artery.

A distal pancreatectomy was performed and because the tumor was not palpated during the intraoperative period and intraoperative ultrasound was not available, the pancreatic cut was

made taking as reference the left border of the superior mesenteric artery due to its proximity to the probable insulinoma of the imaging studies (**Figure 3**).

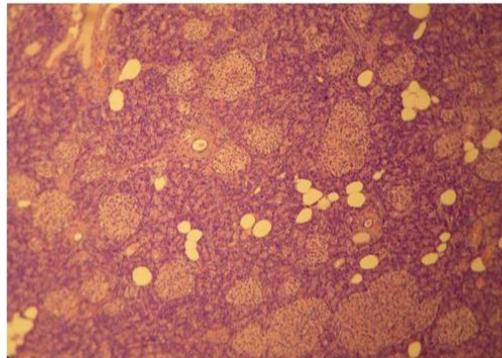


Figure 4. Islets of Langerhans of normal dimensions alternating with hyperplastic islets.

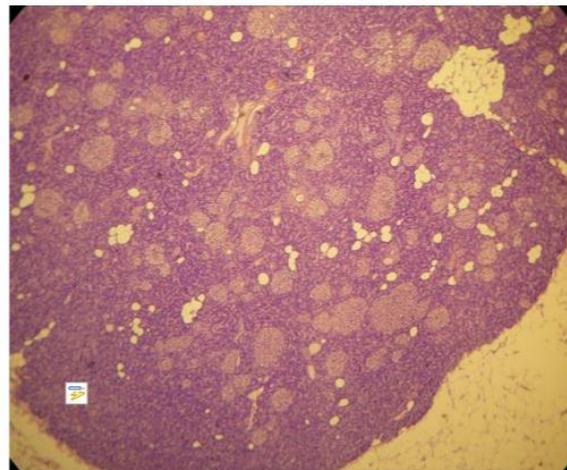


Figure 5. Langerhans islet hyperplasia.

The histopathological study reported diffuse nesidioblastosis (**Figures 4 and 5**). An insulinoma was not located, however an area with a more accentuated islet hyperplasia surrounded by connective tissue of approximately 4 mm in

diameter was observed in the region of the pancreatic head and neck, with hyperplasia in this area being more evident than in the rest of the piece; possibly this would be the lesion visualized in the imaging studies (**Figure 6**). The

patient continued with hypoglycemia, so she was undergoing an additional pancreatic resection, resecting a total of 90% of the organ. The

histopathological study of this surgery only revealed necrosis.

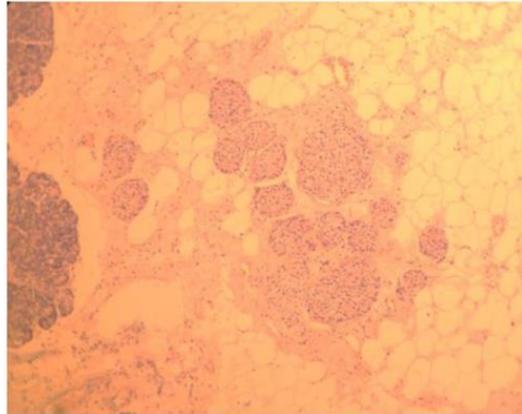


Figure 6. Focus of islets of hyperplastic Langerhans grouped in the region corresponding to the pancreatic head of the piece.

Continuing with hypoglycemia and a low intake, enteral nutrition was initiated, and upon improving its glycemic levels, octreotide and prednisone were added at doses of 0.05 ml and 25 mg respectively, twice a day, showing good evolution. The patient was discharged with better oral intake and continued on octreotide treatment due to continuing intermittent hypoglycemia.

DISCUSSION

Although the current definition of nesidioblastosis specifies a hyperplasia of beta cells^[2], cases of alpha cells have been reported^[10,11,16]. Some authors also call it as the noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)^[3,4].

The pathophysiology is unknown. Although some genes have been identified as Kir6.2, GCK and GLUD1 in infants, in adults their evidence is scarce^[17]; in them it could be a response to a hormonal or metabolic process. One of the hypotheses in infants postulates a dysfunction in the ATP-dependent potassium channels of the beta cell by a mutation in the SUR1 gene^[18]. In adults, one study reported the overexpression of insulin-like growth factor2 (IGF2), the insulin-like growth factor one receptor-alfa epidermal growth factor receptor (IGF1Ra), and the transforming growth factor-beta receptor 3 (TGFRb3) in islets with nesidioblastosis when compared

with tissue samples from benign pancreatic pathologies^[17].

With an incidence of 0.2%^[19] nesidioblastosis in adults occurs mainly after Roux-en-Y gastric bypass^[2,11]; in these patients it has been confirmed by selective arterial stimulation tests with calcium and by histopathological study, and at least 40 cases of nesidioblastosis developed after the bypass have been reported^[5]. In this scenario, the increase of incretins (glucagon-like peptide type 1 (GLP-1) and gastric inhibitory peptide (GIP)) has been implicated as a mechanism of development due to the accelerated transit of nonabsorbed nutrients in the jejunum and the ileum where the L cells are found (producers of GLP-1)^[2,3]. Other possible mechanisms include the lack of reduction of beta cells previously hypertrophied due to obesity, an increase in insulin sensitivity, and an abnormal response of counterregulatory hormones^[3]. Subtotal esophagectomy, subtotal gastrectomy, and Billroth I and II reconstructions have also been associated with NIPHS^[5].

The suspicion of hyperinsulinemic hypoglycemia begins with Whipple's triad (symptoms of hypoglycemia with low serum glucose levels that remit with administration of the glucose)⁽⁵⁾. After ruling out other causes of symptomatic hypoglycemia, the most frequent cause of endogenous

hyperinsulinism is insulinoma [2]. The National Comprehensive Cancer Network (NCCN) establishes that fasting serum glucose levels below 55 mg/dl, an insulin level > 3 mIU/ml, a concentration of C-peptide of at least 0.6 ng/mL and levels of proinsulin of 5 pmol/L or more indicate the presence of an insulinoma. Although the clinical differentiation between insulinoma and nesidioblastosis is almost impossible, the time of hypoglycemia can be taken into account; in insulinoma it occurs during fasting due to the autonomic nature of the insulin secretion of the neoplasm, and in nesidioblastosis the hypoglycemia presents during the postprandial period due to the sustained physiological response [6,7,9,10]. In our patient, symptomatic hypoglycemia events predominated in the early morning, 2 or 3 hours after the last meal.

The somatostatin receptor scintigraphy has a sensitivity of 60% for the detection of insulinoma since approximately only two thirds of them express this receptors, however the expression of the GLP-1 receptors in these tumors exceeds 70%, especially in those with benign behavior, therefore the scintigraphy of GLP-1 receptors allows a more precise localization of small lesions with greater sensitivity and specificity and could discriminate tumor behavior, since these receptors are only expressed in 36% of malignant insulinomas [20]. Another useful imaging study for the differentiation between a focal and a diffuse pattern is PET-CT with dihydroxyphenylalanine (18F-DOPA), in which 96% of diagnostic accuracy is reported in the differentiation between both and 100% for the focal location [21]. The NCCN recommends the ⁶⁸Galium-dotatate PET/CT to locate the insulinoma.

SACST is performed by selective angiography and injection of calcium gluconate into the gastroduodenal, hepatic, splenic, and superior mesenteric arteries; subsequently the level of insulin in the hepatic veins is measured and an increase in it of 2 to 3 times above the baseline value can identify the pancreatic region in which the lesion is located based on the territory of the stimulated artery. For the location of the insulinoma the SACST has a sensitivity greater than 90% and

an accuracy of 88% to 94%. False negatives can be attributed to arterial anatomical variants or to vascular stenoses or shunts, while false positives can be explained by tumor necrosis and calcifications [8]. Although it is a very useful test, in many hospitals it is not available.

The major diagnostic histopathological criteria of nesidioblastosis include the exclusion of an insulinoma by macroscopic, microscopic and immunohistochemical examination, the presence of multiple beta cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm, islets with normal spatial distribution of the various cell types, and no proliferative activity of endocrine cells [3,4,7,22]. As minor criteria have been described the presence of elongated islets, the increase in the number of islets, islets with lobular structure, and macronucleolus in beta cells [23].

The varieties of presentation include focal, diffuse and atypical. Generally, the focal is restricted to an area up to 7.5 mm and the most common location are the body and tail of the pancreas. In the diffuse variety, hyperplasia extends throughout the organ, while the atypical form is characterized by a mosaic pattern in which cells with different morphological characteristics coexist [2]. This classification is generally used for the pediatric population since in adults the diffuse variety predominates and few focal cases have been reported [6]. In this patient, the variety of presentation was diffuse, however, a well-defined area surrounded by connective tissue was identified where the hyperplasia was more pronounced; this region coincided with the location of the tumor in the imaging studies. We found only two similar cases in which an insulinoma was reported by image and nesidioblastosis in the histopathological report [9]. Likewise, there are few reports of cases with synchronous lesions such as mucinous neoplasms, neuroendocrine tumors and microadenomas with nesidioblastosis [10,11,12].

Several drugs have been proposed for nesidioblastosis and until now, none is the best choice as they all have different adverse reactions and do not present the same results. Initially, dietary

regimens with an adequate number of calories accompanied by corticosteroids and octreotide are used [24]. Pasireotide is an analogue of somatostatin that acts on 4 of the 5 somatostatin receptors, presenting an affinity 40 times higher for the SSTR5 compared to other analogues. Due to the suppression of insulin that it causes, hyperglycemia is one of its main adverse effects and therefore would be useful in nesidioblastosis [12]. Another mechanism to inhibit insulin secretion is by blocking the calcium channels in the beta cell membrane; from this group it has been reported that amlodipine is better tolerated since it has fewer adverse effects compared to verapamil and nifedipine [15].

Regarding the extension of pancreatectomy Clancy has suggested that the normalization of glucose levels is achieved by resecting 85% of the pancreas (3); Raffel et al report that the resection of 70% of the organ is sufficient to avoid hypoglycemia [4], and if hypoglycemia persists an almost total pancreatectomy (90%) is very likely to control glucose levels [4] although with this percentage resected up to 40% could develop insulin-dependent diabetes and pancreatic insufficiency [11]. It is estimated that with distal pancreatectomy approximately 50% of patients will be cured without the need for medication and 19% will achieve normoglycemia with the addition of medical treatment [7,11]. Witteles et al. report that resection of 60 to 89% of the pancreas is possibly the most appropriate procedure because the risk of diabetes is less than 10% and it achieves normoglycemia in up to 70% of patients [25].

Other authors suggest conservative resections with additional resections if glycemic control is not achieved [2], and although in the presence of insulinoma in the transoperative period, palpation or ultrasound will identify the tumor in up to 92% of the cases, some authors choose to perform a blindly distal pancreatectomy [10]; On the other hand, Rostambeigi and Thompson do not recommend this practice and prefer to perform SACST [9]. We did not have intraoperative ultrasound or SACST, so based on the location of the tumor in the imaging study we decided to section the pancreas at the level of the left border of the

superior mesenteric. In case of not knowing the location of the insulinoma, an intraoperative histopathological examination with frozen section evaluation for the margins could determine the extent of pancreatectomy in case of having a SACST suggestive of nesidioblastosis. In patients undergoing gastric bypass, the conversion of the Roux-en-Y bypass into a gastric sleeve and/or the restoration of gastric restriction with a gastric band has been described as a surgical treatment for nesidioblastosis [3].

CONCLUSION

There are probably more unreported cases of nesidioblastosis in adults and due to the increase in the incidence of insulinoma we should keep this pathology in mind. Nesidioblastosis should be suspected in hyperinsulinemic hypoglycemia that is difficult to control, in the presence of diffuse patterns in studies of selective arterial stimulation, and when tomography, octreoscan and endoscopic ultrasound can not identify a tumor. Although most agree to resect 60% -80% of the pancreas, the extent of pancreatectomy should be individualized based on the findings of selective arterial stimulation and patient evolution. In case of not locating an insulinoma and having a high suspicion of nesidioblastosis, an intraoperative histopathological examination with frozen section evaluation for the margins could determine the extent of pancreatectomy.

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