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Recurrent hypoglycemia secondary to pancreatic insulinoma

Hipoglucemia recurrente secundaria a insulinoma pancreático

Pablo Salomón Montes-Arcón,* Sandra Herrera-Lomonaco,‡
Paola María Blanco-Pertuz,§ Gloria Caterine Pérez-Mingan§

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Palabras clave:
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ABSTRACT

Pancreatic neuroendocrine tumors are rare neoplasms of erratic behavior, which can be functioning or non-functioning according to their capacity to produce hormones and, therefore, generate diverse symptoms in affected patients; an accurate diagnosis will determine integral management, to improve the patient's quality of life, with emphasis on a complete resection that avoids the presence of residual disease. We present the case of a patient with recurrent hypoglycemic syndrome and imaging studies that showed a tumor lesion in the body of the pancreas, which was surgically operated on with total resection of the lesion, obtaining a diagnosis of pancreatic neuroendocrine tumor (insulinoma) in the pathological anatomy study.

RESUMEN

Los tumores neuroendocrinos pancreáticos son neoplasias poco frecuentes y de comportamiento variable, los cuales pueden ser funcionantes o no de acuerdo con su capacidad para producir hormonas y, por ende, generar diversos síntomas en los pacientes afectados; un diagnóstico certero va a determinar un manejo integral, con el cual se busca mejorar la calidad de vida del paciente, con énfasis en una resección completa que evite la presencia de enfermedad residual. Se presenta el caso de una paciente con síndrome hipoglucémico recurrente y con estudios de imagen que evidenciaron una lesión tumoral en cuerpo de páncreas, la cual es intervenida quirúrgicamente con resección total de la lesión, obteniendo como resultado en el estudio de anatomía patológica el diagnóstico de tumor neuroendocrino pancreático (insulinoma).

INTRODUCTION

Neuroendocrine neoplasms (NEN) are a group of tumors that originate from neuroendocrine cells located in all organs, mainly in the lung, gastrointestinal tract, and pancreas; at the pancreatic level, these lesions have a biological behavior according to their capacity to produce hormones and relatively different clinical management compared to adenocarcinomas; their incidence is less than or equal to one case per 100,000 individuals per year, and they only comprise 1 to 2% of pancreatic neoplasms, their incidence is increasing.[1]

In general, these neoplasms have a sporadic presentation; however, they are also associated with various hereditary entities such as multiple endocrine neoplasias (MEN) type 1, Von Hippel Lindau syndrome (VHL), and neurofibromatosis type 1 (NF-1).[2]

The diagnosis of these pathologies will depend on their functional capacity. Clinically, those with hormone production tend to have an earlier diagnosis and a smaller tumor size compared to non-functioning ones, in which the diagnosis is mainly due to incidental findings through imaging studies motivated by other causes unrelated to the lesion.[3]

* Second-year resident, postgraduate in Pathology. ORCID: 0000-0003-3021-0319.
‡ Lecturer, Department of Pathology.
§ Second-year resident, postgraduate in Internal Medicine.

University of Cartagena. Cartagena, Colombia.

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Within the pancreatic NEN, insulinomas are the pancreas' most common functioning endocrine neoplasm. Their main symptom is hypoglycemia, and their etiology is unknown, they occur in one to four persons per million in the general population, can be seen at any age, with an equal gender distribution; up to 90% of insulinomas are benign, 90% are solitary, > 90% occur in intrapancreatic sites, and 90% are < 2 cm in diameter, their distribution is uniform throughout the pancreas. Extrapancreatic localization is rare (incidence < 2%) with a higher frequency of wall duodenum; 90% occur in intrapancreatic sites, and 90% are < 2 cm in diameter; their distribution is uniform throughout the pancreas, and extrapancreatic location is rare (incidence < 2%) with greater frequency in the duodenal wall.[4]

PRESENTATION OF THE CASE

A 47-year-old female patient with no relevant personal or family history was referred from a less complex hospital for a clinical picture of 15 months of evolution due to recurrent episodes of asthenia, adynamia, pallor, and diaphoresis, including loss of consciousness, with documentation of glycemic levels below 40 mg/dl; these clinical manifestations entirely resolved after administration of unquantified glucose.

Due to severe and recurrent hypoglycemia not associated with the intake of antidiabetic or exogenous hypoglycemic agents, a 72-hour fasting test was performed with measurement of glucose and insulin levels, confirming hypoglycemia with normal insulin levels; a tomography of the skull and sella turcica was performed without finding lesions; However, an abdominal CT scan showed the presence of a focal increase in the size of the adrenal gland, so it was decided to characterize with MRI of the abdomen in which a single focal lesion of 13 × 10 mm was identified at the junction of the pancreatic body and tail *(Figure 1)*, described as hypointense in T1 sequences fat saturation techniques (FAT SAT), slightly hyperintense in T2 sequences with discrete peripheral enhancement after contrast administration and restriction in diffusion-weighted magnetic resonance imaging (DWI) sequence and an apparent diffusion coefficient (ADC) map.

She was evaluated by the endocrinology group, considering a neuroendocrine tumor in the pancreas; paraclinical and tumor markers were requested that showed positivity for chromogranin A of 412 ng/ml *(Table 1)*; due to recurrence and persistence of hypoglycemia despite high metabolic flows, it was decided to perform a distal pancreatectomy by laparoscopy through which a single 1.5 cm tumor located in the body of the pancreas was found and removed. The specimen was subsequently sent to the pathology department.

Pathology analysis revealed the presence of a pancreatic neuroendocrine tumor compatible with insulinoma from the submitted clinical history; the diagnosis was confirmed after performing the relevant immunohistochemistry studies *(Figure 2)*.

After the procedure, the patient evolved asymptomatic, without new episodes of hypoglycemia after several days of observation, the reason for which she was discharged with the indication for outpatient follow-up. She

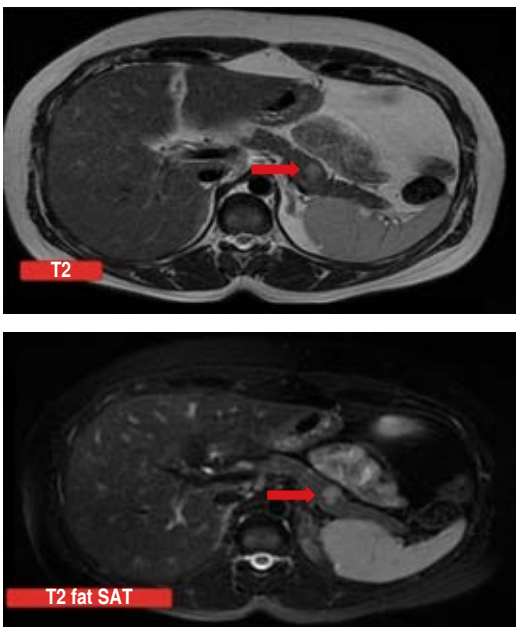

Figure 1: *Gadolinium-contrast MRI in a T2 and fat T2 sequence showing a 12.2 × 9.7 mm tumor lesion in the pancreatic body.*

Table 1: Paraclinical tests performed during the patient's hospital stay, among which the elevated value of the tumor marker chromogranin A stands out.

09/13/2021	
Gastrin, pg/ml	10.3*
Free insulin, ImU/l	14.8*
PTH intact molecule, pg/ml	35*
Total triiodothyronine, ng/ml	0.7*
Total thyroxine, ug/dl	7.2*
TSH, IU/ml	2.83*
HB AC1, %	5.2*
White blood cells, %	8,300
Neutrophils	75
Lymphocytes	15
Hemoglobin, g/dl	10.6
Hematocrit, %	38
VCM, um^3	70
HCM, pg	19
MHC, g/dl	28
EDI, %	19
Platelets, mm^3	363,000
09/15/2021	
Chromogranin A, ng/dl (range)	412 (0-100)
Natriuretic peptide B, pg/dl	2.25*

PTH = parathyroid hormone. TSH = thyroid stimulating hormone. HB = hemoglobin. MCV = mean corpuscular volume. MCH = mean corpuscular hemoglobin. MCHC = mean corpuscular hemoglobin concentration. EDI = erythrocyte dispersion index.
* Normal values.

was evaluated at an outpatient clinic one month after her discharge without evidence of new episodes of hypoglycemia. She was asymptomatic, and the contrasted abdominal tomography follow-up scan showed no residual lesions, with changes secondary to her surgical intervention; she was indicated to continue medical follow-up every three months.

DISCUSSION

The diagnostic and therapeutic approach to this entity should be multidisciplinary. The initial approach should be performed by a specialist in endocrinology who knows the management guidelines, added to a good radiology service that establishes the presence of the lesion and its delimitation so that in case there is the possibility of resection, the procedure is performed by a highly qualified surgical group that guarantees good oncological results.[5]

In patients with insulinoma, episodes of hyperinsulinemic hypoglycemia cause various autonomic and neuroglycopenic symptoms, usually appearing on an empty stomach. Documentation of the so-called Whipple's triad, i.e., symptoms consistent with hypoglycemia, low plasma glucose measured at the time of symptoms, and immediate relief of symptoms after glucose administration, is the cornerstone of the diagnosis of insulinoma.[6]

Demonstration of concomitant low plasma glucose with inappropriately high serum insulin and C-peptide levels in a symptomatic patient forms the basis for biochemical diagnosis, with the exclusion of other causes of hyperinsulinemic hypoglycemia; B-hydroxybutyrate levels of 2.7 mmol/l or less, an increase in plasma glucose of at least 1.4 mmol/l after intravenous glucagon administration, and a negative detection of oral hypoglycemic agents distinguish endogenous hyperinsulinemic hypoglycemia from that caused by other mechanisms.[7]

A 72-hour fasting test with plasma glucose, insulin, and C-peptide measurements is considered the gold standard for the biochemical diagnosis of insulinoma.[6]

Dynamic gadolinium-enhanced magnetic resonance imaging (MRI), three-phase computed tomography (CT) scan, and endoscopic ultrasonography (EUS) have been considered the most useful imaging modalities for the evaluation of insulinomas; in experienced hands, the sensitivity of EUS is 70-95% and in combination with three-phase CT, sensitivities of up to 100% have been reported.[8]

The cornerstone for complete resection of the lesion is surgical treatment. Laparoscopic surgery with intraoperative ultrasound confirmation of the location of the lesion is preferred, considering the inherent advantages of minimally invasive surgery (less postoperative pain, shorter hospital stay, better cosmetic results, reduced morbidity), but

open surgery can also be used without being contraindicated.[9]

Despite the characteristic clinical behavior of insulinomas, diagnostic confirmation should always be made by anatomic pathology; these lesions are characterized at the macroscopic level as solitary, well-demarcated lesions with a homogeneous, tan-yellow cut surface with or without hemorrhage.[5] Microscopically, monotonous cells showing round nuclei with salt/pepper chromatin and abundant cytoplasm arranged in a trabecular, nested, cribiform, or solid architecture are characteristic.[10]

Immunohistochemical labeling is extremely useful. Stains to be used include neuroendocrine markers such as synaptophysin, chromogranin A, insulin gene enhancer protein ISL-1, proinsulin, amylin, and islet amyloid polypeptide to confirm the suspicion, in addition to the Ki-67 cell proliferation index and epithelial markers to rule out lesions such as cytokeratin cocktails.[11]

In addition to the conventional study, genetic analysis should be performed in patients with early onset of these lesions, mainly recommended in patients under 30 years of age, to rule out the involvement of hereditary clinical syndromes such as multiple endocrine neoplasias (MEN) type 1, Von Hippel Lindau syndrome (VHL) and neurofibromatosis type 1 (NF-1) and to help screen the patient for synchronous lesions of another nature.[12]

The prognosis of these patients in the postoperative period is generally good; however, some factors have been described that are related to a less favorable evolution, among which tumor size greater than 2 cm, high Ki-67 labeling index, and high mitotic count stand out. Despite these, malignant

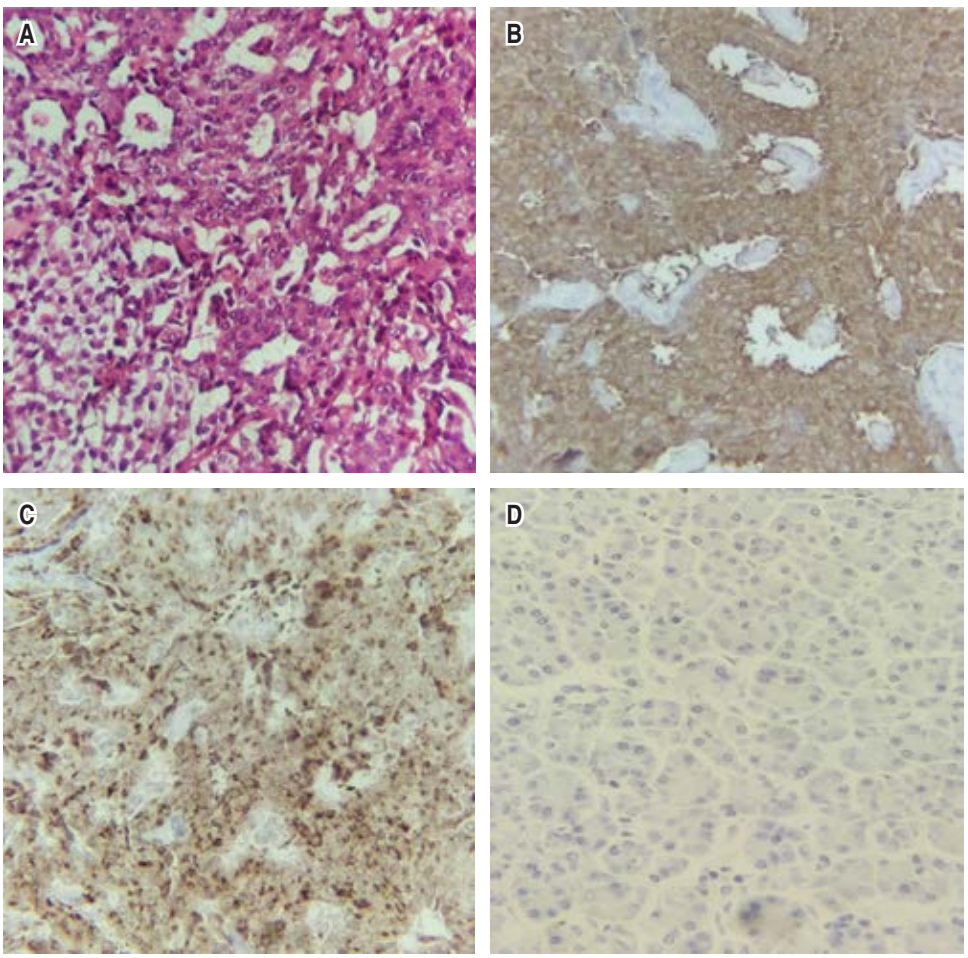

Figure 2:

A) *Tumor lesion consisting of small to medium-sized cells with eosinophilic to amphophilic and firmly granular cytoplasm, uniform, central, oval nuclei, with chromatin arranged in a "salt and pepper" pattern, which are arranged in a cribriform pattern, with a rich vascular network; in other areas, cells with clear and vacuolated cytoplasm are seen.* ***B-C)*** *Cytoplasmic positivity for immunohistochemical markers synaptophysin and chromogranin.* ***D)*** *Low Ki-67 proliferation index, less than 5% of the tumor volume.*

insulinomas are frequently grade 2 according to the World Health Organization classification.[13]

CONCLUSION

Despite its low incidence, insulinoma is the most frequent neuroendocrine neoplasm of the pancreas susceptible to curative surgical treatment, so its recognition and timely management is of vital importance; for the patient's approach, the multidisciplinary approach will allow better management decisions and, therefore, more favorable oncologic results with improvement in the patient's quality of life.

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Correspondence:
Pablo Salomón Montes-Arcón
E-mail: pmontesarcon@gmail.com