REVISTA COLOMBIANA de Endocrinología Diabetes & Metabolismo

CASE REPORT

Epilepsy-mimicking pancreatic insulinoma

Insulinoma de páncreas que imita epilepsia

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Abstract

An insulinoma is a rare secretory endocrine neoplasm that causes a hypoglycemic hyperinsulinemic state derived from the absence of endocrine regulation of insulin secretion. Its worldwide incidence is 1 to 5 cases per million individuals every year. Neuroglycopenic and sympathetic adrenal symptoms are the most common clinical manifestations. Also, diagnosis is established by Whipple's triad, together with the finding of inappropriately high levels of insulin, C peptide, proinsulin, and beta-hydroxybutyrate. Surgical resection is the first line of management choices, given its benign features and high recovery rates. The aim of this report is to present the case of male patient with a history of misdiagnosed epilepsy refractory to anticonvulsant management, who presented with an episode of severe hypoglycemia and was subsequently diagnosed with insulinoma that improved with surgical management.

Keywords: *Hyperinsulinism; Hypoglycemia; Insulinoma.*

Resumen

El insulinoma es una neoplasia endocrina funcional rara, que provoca un estado hiperinsulínico hipoglucémico derivado de la ausencia de regulación endocrina de la secreción de insulina. Su incidencia es de 1 a 5 caso por millón de personas al año a nivel mundial. Es la sintomatología más comúnmente manifestada por síntomas neuroglucopénicos y simpaticoadrenales. El diagnóstico se establece por la tríada de Whipple, los niveles elevados de insulina, el péptido C, la proinsulina y los niveles disminuidos de betahidroxibutirato, además de descartar el uso de sulfonilureas. El manejo de elección es la resección quirúrgica, dado su alto nivel de benignidad y curación total. Se presenta el caso de un hombre en manejo anticonvulsivante por epilepsia con refractariedad de síntomas, quien debutó con cuadro de hipoglucemia grave necesaria para el diagnóstico de insulinoma, con manejo quirúrgico y resolución del cuadro de base.

Palabras clave: hiperinsulinismo, hipoglucemia, insulinoma.

Introduction

Insulinomas are neuroendocrine tumors that cause a hyperinsulinemic hypoglycemic state due to deregulated insulin production by the pancreatic beta cells. Normal insulin blood levels range between 3.5 and 5.5 mmol/L (1, 2). Insulinomas are rare, with an incidence of 1 to 3 cases in 1 million habitants per year, and they are most common in the 5th decade of life, with a ratio of 3:2 female predilection (2-4). They are the most common secretory pancreatic tumors, corresponding to 25% of its kind and accounting for 1 to 2% of all pancreatic neoplasms. Furthermore, 90% of insulinomas are considered benign, 90% are solitary, and more than 90% have an intrapancreatic location; 90% are less than 2 centimeters in diameter and the most common extrapancreatic location is the duodenal wall (5).

Clinical manifestations are divided into two categories: autonomic symptoms due to sympathetic stimulation, such as palpitations, tachycardia, tremor, and anxiety, as well as symp-

toms due to cholinergic stimulation such as diaphoresis, increased appetite, salivation, and nausea; and neuroglycopenic symptoms such as altered mental status, confusion, dysarthria, seizures, focal neurologic signs, and coma. Diagnosis is based on the presence of Whipple's triad (hypoglycemia, manifestations of the symptoms mentioned above, and symptom resolution with glucose administration), and laboratory tests. Also, insulinoma-related hypoglycemia may occur after meals (5-7). The expected laboratory findings include serum insulin levels >3 µU/mL, which is an inappropriate elevation in the context of hypoglycemia, along with other markers that indicate an increase of endogenous insulin secretion, such as C-peptide levels >0.6 ng/mL, proinsulin levels >5.0 pmol/L and beta-hydroxybutyrate <2.7 mmol/L when fasting glucose is < 55 mg/dL.

We present the case of a 39-year-old male with a history of epilepsy treated with antiepileptic drugs, whose final diagnosis was an insulinoma, which resolved after tumor resection.

Case report

A 39-year-old male from a rural area in southern Colombia with a prior history of mild cognitive impairment seen in a private clinic. He had experienced tonic-clonic seizures and loss of consciousness for four years and was, therefore, assessed in the neurology department with a diagnosis of epilepsy. He was later prescribed levetiracetam 1000 mg every 24 hours, with no significant improvement. Upon further questioning on a follow-up visit, the patient mentioned that his symptoms improved with the consumption of a refined form of sugarcane known as "panela" which he carried with him at all times, but no further work-up was performed in the outpatient setting.

The patient was admitted to the hospital due to an episode of altered mental status and generalized tonic-clonic seizures that lasted 3 minutes approximately, and was found to have a fingerstick glucose of 25 mg/dL. Despite the administration of benzodiazepines and 10% dextrose boluses, the patient could not recover consciousness and developed respiratory depression requiring intubation and Intensive Care Unit (ICU) admission. Later, the patient showed some improvement with an infusion of 50% dextrose at a rate of 7 to 10 grams per hour.

Laboratory results showed central glucose of 25 mg/dL, hyperinsulinemia with a value of 130.3 µUI/L (2.6-25 µUI/L), increased C-peptide 8.4 ng/mL (1.1-4.4 ng/mL), pro-insulin of 9.4 pmol/L (≤18.8 pmol/l) and levels of anti-insulin antibodies -0.10 (<-0.95) interpreted as negative as was also the case with serum levels of sulfonylureas such as glyburide, gliclazide, glimepiride, gliquidone, glipizide, and tolbutamide.

Abdominal Magnetic Resonance Imaging (MRI) revealed a focal hypo-intense mass lesion measuring 27×24 mm in the tail of the pancreas, with late-phase peripheral contrast enhancement.

While in the ICU, the patient developed ventilator-associated pneumonia and catheter-related bacteremia due to *Staphylococcus haemolyticus*, that was successfully treated with antibiotics. Surgical resection of the tumor was proposed following the hepatobiliary surgery consult. The patient received a pneumococcal vaccine due to the possibility of an eventual splenectomy depending on the extension of the pancreatic tumor.

After 12 days of hospital stay, the patient was taken to the operating room. A subcostal incision (Chevron approach) was done, and surgical resection of the mass was performed without any complications. The surgery report included resection of a 3×3 cm tumor located in the neck of the pancreas with extension to the splenic vessels. The studied areas and the retroperitoneum were clear of lymphadenopathy. The patient was discharged three days later with no symptoms or complaints. On follow-up, the patient has remained symptom-free. Histopathologic examination of the surgical block revealed a grade 1 (WHO classification) well-differentiated pancreatic endocrine tumor, with peri-pancreatic adipose tissue infiltration, lymph vascular invasion, and local lymph node involvement. Margins were clear of neoplastic cells (**Figures 1** and **2**).

Discussion

An insulinoma is a rare condition in which there is abnormal insulin production by pancreatic beta cells. It has a low incidence ranging from 1 to 5 per million people (3), and low metastatic involvement reported at less than 10% (8). The first descriptions were made in 1927, consisting of severe hypoglycemia episodes in patients with surgical findings of a fatal tumor of pancreatic islet cells (9). Clinical manifestation occur in 73% of people in a fasting state, with a full spectrum of neuroglycopenic-type symptoms, which may or may not be preceded by adrenal (autonomic) sympathetic symptoms. The initial diagnostic approach could be challenging because insulinomas can also mimick episodes of confusion, epilepsy, and nightmares, all the way to neuropsychiatric disorders (10-12). The average duration of symptoms before diagnosis is less than 1.5 years. However, there are reports of patients who remain asymptomatic for decades. It has also been found that up to 20% of patients have been initially diagnosed with a neurological or psychiatric disorder (13). Increased glucose uptake by muscle, liver, and adipose tissue in addition to an inhibition of the gluconeogenesis and glycogenolysis pathways play an important role in the deranged pathophysiological state of hyperinsulinism, leading to altered brain function as a result of a drop in the primary substrate, with the possibility of cellular damage due to increased lactate in alternative pathways (1).

Similar to what happened in this case, the initial diagnosis is wrong in many patients because of the neuroglycopenic

Figure 1. A. HE 4X Normal pancreatic parenchyma observed in the right half, with a neoplasic lesion observed in its well-defined left part, consisting of well differentiated nests of cells. B. HE 10X Solid nests of polygonal cells with salt-and-pepper chromatin nuclei. C. HE 40 X. Polygonal cells with salt-and pepper-nuclei. D. Lymph node metastasis.

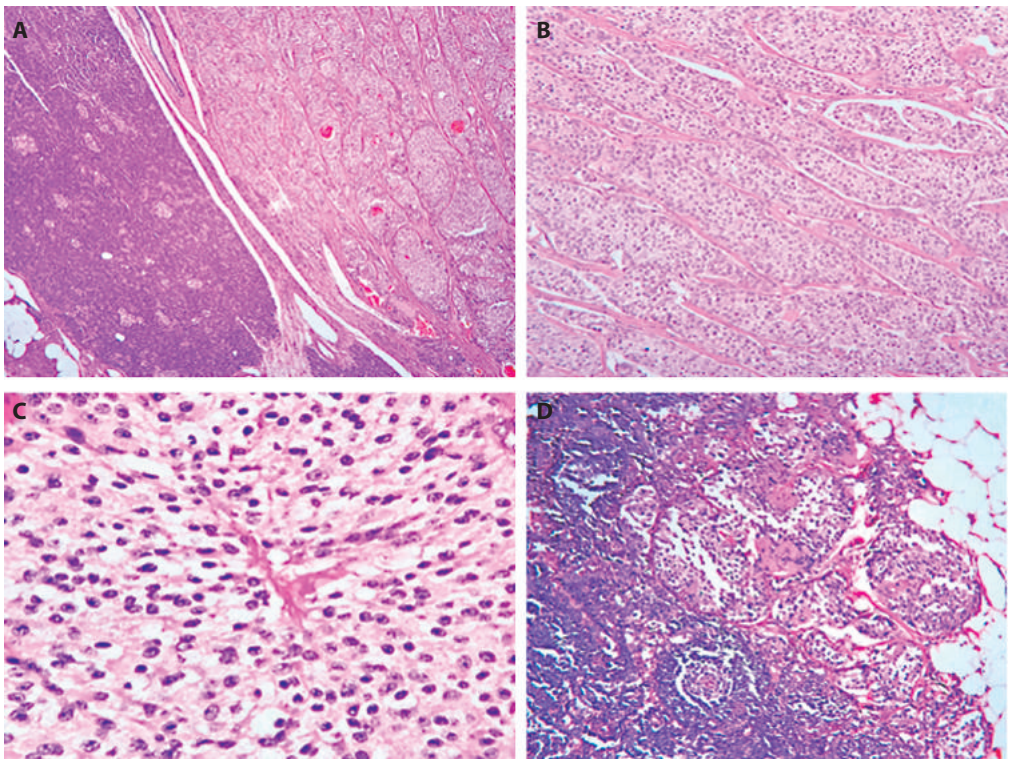
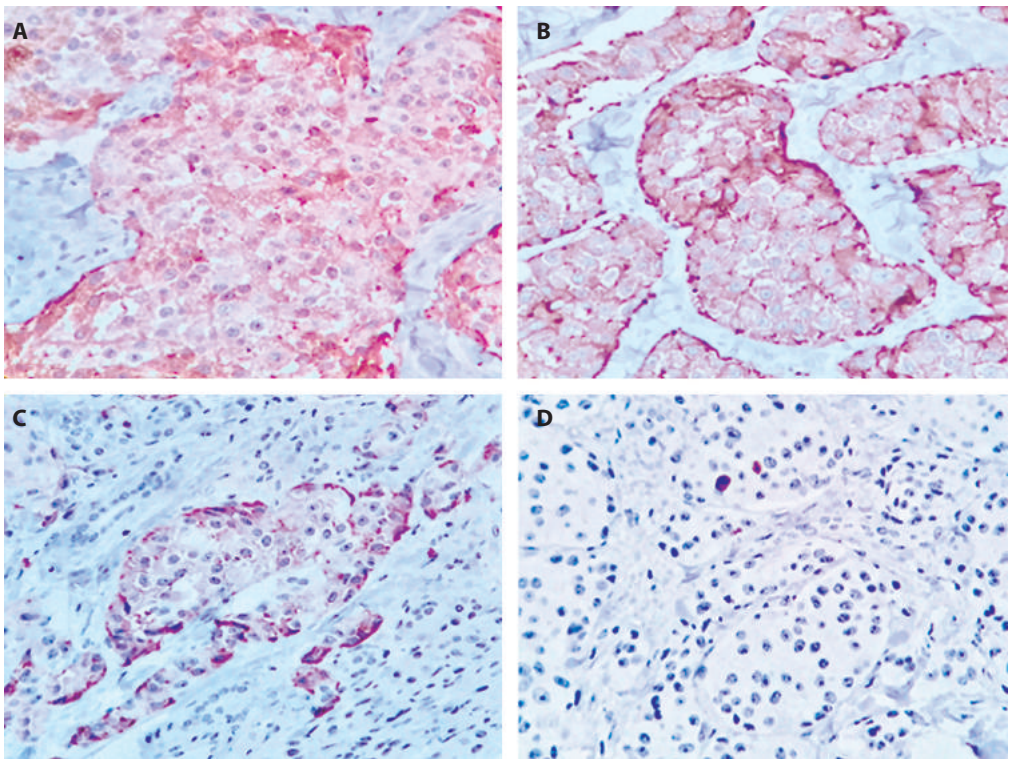


Figure 2. A. Chromogranin positive, **B.** Synaptophysin positive, **C.** Positive insulin marker, **D.** Low proliferation Ki- 67 marker.



symptoms with neurological and psychiatric manifestations, mistaken for epilepsy because of the similar symptomatology. This results in delayed insulinoma diagnosis, with delayed initiation of adequate management (14). This is compounded by the fact that symptoms lack specificity and could be overlooked if glucose levels are not documented, and those levels may even be normal given pulsatile insulin secretion (15). Clinically, ignorance of hypoglycemia is common in patients with insulinomas due to adaptations to a chronic hypoglycemic state that involves increased glucose transport efficiency across the blood-brain barrier. Neuroglycopenic symptoms are the result of inadequate glucose use by brain tissues and can be exceptionally vague and go unnoticed. However, if not addressed on time, mild symptoms can progress due to the most severe neuroglycopenia findings, and a potentially curable disease may result in severe neurological injuries, including coma and death (16).

Insulinoma diagnosis is based on Whipple's triad and the presence of elevated serum concentrations of insulin, C-peptide, and proinsulin, and decreased levels of beta-hydroxybutyrate (17) once the use of sulfonylureas has been ruled out. As for imaging diagnosis, locating the tumor is challenging due to its small size (18). For that reason, multiple imaging modalities may be necessary, computed tomography (CT), MRI, ultrasonography, and positron emission tomography being very useful. However, CT is the most widely used modality because of its availability and high sensitivity. In this study of a patient with a 4-year clinical course mistakenly diagnosed as having epilepsy, antiepileptic medications were given during a prolonged period without improvement. Diagnosis was subsequently made when the patient presented with severe hypoglycemia. Therefore, a delay in diagnosis may result in unnecessary treatment for epilepsy or other psychiatric disorders. Also, medical staff must be aware of the importance of assessing the metabolic causes of seizure disorders. Finally, the majority of these tumors are benign and surgical resection is curative with low recurrence rates (19), as was the case with our patient in whom the tumor was resected without any complications, with symptom resolution to this date.

Conclusion

Insulinomas are rare, mostly benign tumors. A high index of suspicion is necessary, considering that diagnosis may be delayed due to confounding neuropsychiatric findings such as epilepsy. We showed the case of a male patient diagnosed with epilepsy and treated with antiepileptic medications for an underlying neuroendocrine tumor which was ultimately surgically resected, leading to a favorable outcome.

Conflict of interest

No external funding was received for this article.

Ethical considerations and informed consent

The patient agreed to the use of his data for writing this report by signing an informed consent form, provided his anonymity was protected at all times.

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