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CASE REPORT

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Impaired glucose tolerance with neurological manifestations in insulinoma

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Abstract

Insulinoma may have an atypical presentation and it should be suspected in patients with neurological manifestations in spite of an atypical insulin and proinsulin levels associated with hypoglycemia. Fast test is an important tool to reach the diagnosis.

KEYWORDS

hypoglycemia, insulinoma, neurological symptoms, proinsulin

1 | INTRODUCTION

We present the case of a patient with neurological symptoms that may be confused with those of epilepsy. We documented low insulin and proinsulin levels, and the diagnostic work up was compatible with insulinoma. Borderline levels of insulin and proinsulin in hypoglycemia do not rule out insulinoma.

Insulinoma may have an atypical presentation and investigations are not always conclusive, which makes a diagnosis rather difficult in many cases.

Insulinoma should be suspected in patients with neurological manifestations in spite of atypical insulin and proinsulin levels associated with hypoglycemia.

Pancreatic insulinoma (PI) is a rare cause of hypoglycemia in patients without diabetes mellitus and approximately 90%–95% of these tumors are solitary and benign.[1]

The diagnosis of insulinoma usually requires having recurring episodes of hypoglycemia, inappropriate secretion of insulin and C-peptide. Confirming the diagnosis of insulinoma remains challenging despite improvements in chemical, imaging, and histological techniques.[2]

Therefore, it is important to consider insulinoma, particularly in patients presenting with fasting hypoglycemia associated with neurological manifestations.[3]

There are several reports of insulinomas misdiagnosed as epilepsy.[4]

We present an interesting case of a patient with neurological symptoms caused by hypoglycemia with normal fasting glucose levels and a 5-h oral glucose tolerance test (OGTT) without a clear clinical pattern of insulinoma but with an abdominal computed tomography (CT) compatible with this entity.

2 | CASE REPORT

A 50-year-old woman without a relevant medical history, during previous 4 years, was presented with brief episodic neurological symptoms such as loss of consciousness with hypotonia and bladder incontinence, confusion, crying, and amnesia to recent events. She recovered fully within 20 min after food intake. These episodes could occur at any time of the day without an identifiable trigger.

Before consulting with us, she had laboratory work up that included fasting glucose, insulin, C-peptide levels, and OGTT. She was diagnosed as having reactive hypoglycemia and treated with fractionated diet during the day. Despite following the dietetic advice, she continued to experience the same intermittent symptoms. Her physical and neurological examinations were normal, and her body mass index was 23 kg/m^2.

The electroencephalogram (EEG) showed epileptic activity and slowing in the frontal and left anterior temporal region, with phase reversal at F7 that did not change with intermittent photic stimulation or hyperventilation. Antiepileptic medication with levetiracetam was ineffective after 3 months of treatment.

Routine laboratory tests and relevant results were obtained. Fasting blood glucose (74 mg/dl), creatinine (0.74 mg/dl), corrected calcium (9.8 mg/dl) (8.6–10.3), TSH (3.71 UI/ml), cortisol AM (7.71 µg/dl), Prolactin 15.2 ng/ml (5.18–26.53), and HbA1c (4.7%). Liver and kidney function test results were normal.

Glucose intolerance was diagnosed after a 5-h OGTT was obtained (Table 1). Seizures were also related to fasting; therefore, a 72-h fast test was performed. Seven hours after the fast test was initiated, the patient presented symptomatic hypoglycemia, without suppression of insulin or proinsulin (Table 2).

An abdominal CT scan revealed a 8 mm pancreatic distal body tumor (Figure 1).

A transendoscopic ultrasound was performed and it showed a well defined 7 × 4 mm hypoechogenic lesion in the body of the pancreas adjacent to the main pancreatic duct.

The patient underwent distal pancreatectomy, and, in this case, splenectomy was performed due to an injury at the level of splenic hilum.

The final pathology report showed well-differentiated 6 × 5 mm endocrine tumor located at the distal body of the pancreas. Immunohistochemistry was positive for chromogranin A, synaptophysin and insulin, cellular proliferation index 1% (Ki67/MIB-1) (Figures 2 and 3); negative surgical margins and, the absence of lymphovascular invasion and perineural and extrapancreatic extension. The TNM classification was T1, N0, and M0. The ENETS Consensus Guidelines Update stage was G1 because the tumor had Ki67 1%.[5]

TABLE 1 Five-hour OGTT

Time	Glucose (mg/dl)	Insulin (µUI/ml)
0 min	68	1.78
30 min	129	26.87
60 min	171	36.13
2 h	157	28.57
3 h	152	16.06
4 h	81	1.84
5 h	53	1.91

Note: Glucose elevation of 152 mg/dl after 2 h of the 75 g sugar load followed by a glucose decrease of 53 mg/dl. Lack of late recovery of hypoglycemia is suggestive of insulinoma, unlike what occurs in reactive hypoglycemia.

Before surgery, our patient did not receive medical treatment with mTOR inhibitors, somatostatin analogs, or diazoxide. The aforementioned symptoms completely disappeared after surgery.

We did suspect multiple endocrine neoplasia type I (MEN-1) or Wermer's syndrome but we ruled it out because there was no evidence of pituitary or parathyroid dysfunction.

Two years after surgery, the patient remains asymptomatic and not on any medications, and the glucose tolerance test is normal.

3 | DISCUSSION

In our patient, there are relevant clinical data that led us to suspect that the seizures that she presented were due to metabolic alterations due to hypoglycemia, such as those presented in fasting state. Before arriving with us, she had already undergone fasting glucose, insulin, C- peptide levels, and OGTT levels suggesting reactive hypoglycemia and treated with a fractional diet during the day. In order to avoid reactive hypoglycemia and in spite of being on a fractionated diet during the day, our patient continued having intermittent neurological symptoms. Because of this, further testing was performed, leading us to the diagnosis of insulinoma.

Because of the uncommon and diverse symptoms of insulinoma, its diagnosis was often overlooked.[6] Clinical suspicion is the key for making the diagnosis. The 72-h fast test is the current gold standard to establish a qualitative diagnosis.[1] Because this test requires hospitalization for at least 72 h, carries inherent risks, and is stressful for some patients, alternative tests for the diagnosis of insulinoma have been developed. One of them is the prolonged OGTT, for which some reports have demonstrated that the induction of severe hyperinsulinemia followed by significant hypoglycemia can be useful for the diagnosis of insulinoma.

TABLE 2 Seventy-two-hour fast test

Variable	Values obtained after 7 h of fasting	Values for the suspicion of insulinoma
Blood glucose	38	≤40 mg/dl
Insulin	3.78	>3 μU/ml
C-Peptide	0.93	≥0.2 ng/dl
Proinsulin	4.78	≥5 pmol/L
Beta-hydroxybutyrate	0.21	≤2.7 mmol/L
Circulating oral hypoglycemic agents	No	No
Insulin to C-peptide ratio	0.08	<1.0

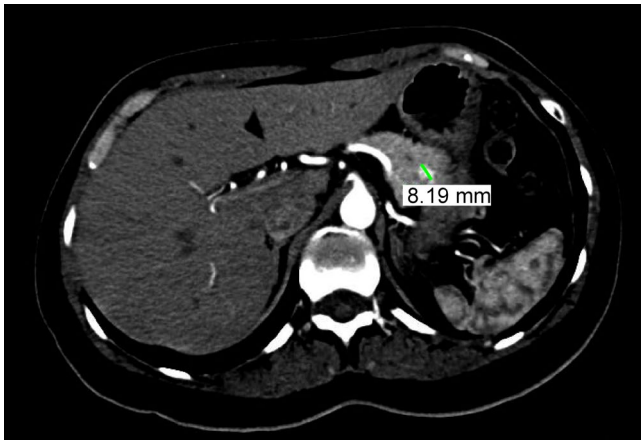

FIGURE 1 Abdominal CT scan showing a hypervascular neoformation mass measuring 8 mm in the body of the pancreas. Intravenous contrast revealed an intense arterial enhancement which remained isodense in simple and delayed phases. The rest of the pancreas presented a preserved morphology. Based on the radiographic and clinical characteristics, a neuroendocrine tumor was considered

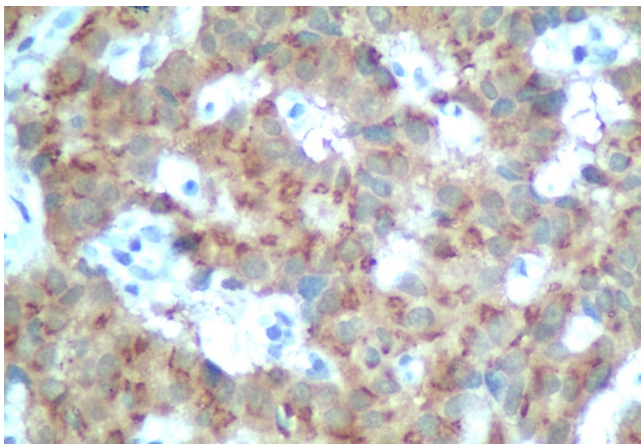

FIGURE 3 Tumor cells stain positively for insulin

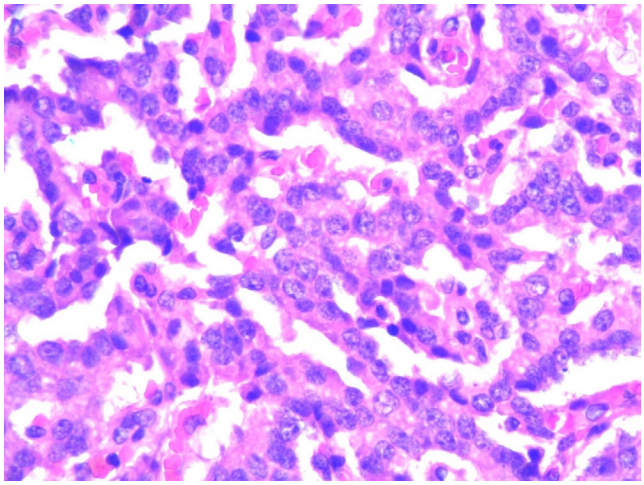

FIGURE 2 Well-differentiated neuroendocrine tumor with trabecular pattern and monomorphous cytoplasmic-reach cells (H-E)

Li et al. evaluated patients with PI 15 patients with PI and 12 patients with reactive hypoglycemia. All patients underwent a 5-h OGTT. As previously described in other reports, patients with insulinoma presented with low glucose and elevated insulin at the fasting and 5-h postload timepoints. Patients with reactive hypoglycemia had a normal fasting glucose and insulin and suppressed insulin after the hypoglycemic episode.[7] Interestingly, during the OGTT, our patient suppressed insulin secretion during hypoglycemia; for example, at the 5-h postload timepoint, her glucose level was 53 mg/dl, and her insulin level was 1.91 μU/ml.

The glucose values obtained in our patient after the 2-h postload timepoint in OGTT suggested carbohydrate intolerance[8] and did not display a clear pattern of insulinoma. Nevertheless, the 72-h fast test results were compatible with insulinoma in most of the values. Few reports have established the relation between insulinoma and glucose intolerance and/or diabetes.[9–11]

Insulin to C-peptide ratio is used to distinguish between hypoglycemia caused by exogenous insulin and that caused by insulinoma, because C-peptide only forms when endogenous insulin is activated. With exception of patients receiving exogenous insulin and patients with liver cirrhosis, insulin to C-peptide ratio in a normal healthy living person never exceeds 1.0. An insulin to C-Peptide ratio >1.0 is related, hypoglycemia to exogenous insulin and a insulin to C-Peptide ratio <1.0 related to insulinoma. Our patient

had an insulin to C-Peptide ratio 0.08, compatible with insulinoma.

The proinsulin criterion of 5 pmol/L or higher provided 100% sensitivity and a specificity of 68%–78%. Guettier et al.[12] suggested that a proinsulin concentration of ≥22 pmol/L at end of fasting test best discriminates cases of insulinoma from controls; however, even in the absence of elevated levels of proinsulin, insulinoma should be ruled out. In general, the workup for insulinoma consists of several fasting glucose/insulin values, an OGTT, and the rapid test.

This case illustrates the importance of the OGTT and the rapid test in the diagnosis of insulinoma. Interestingly, fasting glucose was only low-norma. At the end of OGTT, insulin and proinsulin values decreased; however, in the final values of the rapid test, the insulin and proinsulin values did not drop to the expected cut-off points during hypoglycemia.

4 | CONCLUSION

Even in the absence of elevated levels of proinsulin, insulinoma should be considered. Patients with an insulinoma may not fulfill all the established criteria during a 72-h fast test, and the clinical history continues to be the pathway for further testing that can help us to support or rule out insulinoma.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

LGV-R: evaluated and assessed the clinical status of the patient during the different phases of the disorder, wrote and reviewed the paper. AAR-A: evaluated and assessed the clinical status of the patient during the different phases of the disorder, selected the literature, corrected and reviewed the paper. AÁ: reviewed and wrote the pathology findings, literature review. EC: reviewed and wrote the neurophysiology findings, assessed the neurological status of the patient during the different phases of the disorder, reviewed the paper. JL: selected the patient, assessed the clinical status of the patient during the different phases of the disorder, wrote and reviewed the paper.

ETHICAL APPROVAL

Ethics approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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