

DIFFICULT CASE

High-Dose Calcium Stimulation Test in a Case of Insulinoma Masquerading as Hysteria

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It is reported that some cases with insulinoma present with neuropsychiatric symptoms and are often misdiagnosed as psychosis. Here we report a case of insulinoma masquerading as hysteria, whose final diagnosis could be made using high-dose calcium stimulation test. A 28-yr-old woman was referred presenting with substupor, mutism, mannerism, restlessness, and incoherence. Laboratory examinations revealed hypoglycemia (33 mg/dL) and detectable insulin levels (9.7 μ U/mL), suggesting the diagnosis of insulinoma. However, neither imaging studies nor selective arterial calcium injection (SACI) test with a conventional dose of calcium (0.025 mEq/kg) indicated the tumor. High-dose calcium injection (0.05 mEq/kg) evoked insulin secretion when injected into superior mesenteric artery. A solitary tumor in the head of the pancreas was resected, and her plasma glucose returned to normal. Postoperatively, iv injection of secretin resulted in a normal response of insulin, which was not found preoperatively. This case suggests the usefulness of the SACI test with high-dose of calcium in the case of insulinoma when the standard dose fails to detect such a tumor.

Key Words: Insulinoma; hysteria; selective arterial calcium injection test; secretin test.

Introduction

Insulinomas are often initially found with hypoglycemic symptoms, such as adrenergic (sweating, palpitation, or weakness) and neuroglycopenic (confusion, amnesia, or seizures) symptoms (1). It is reported that some cases with insulinoma present with neuropsychiatric manifestations and are often misdiagnosed as psychosis (1–3). The tumor is often undetectable with conventional imaging studies such as abdominal

ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). The selective arterial calcium injection (SACI) test is generally required for both the diagnosis of insulinoma and the preoperative localization (4–10). Some studies claimed that the SACI test localized insulinomas correctly in all cases (4–9), whereas others showed that localization of tumors was unsuccessful even with the SACI test (10,11). Here we report a case of insulinoma masquerading as hysteria in which localization was not achieved by selective arterial injection of a standard dose of calcium (0.025 mEq/kg of Ca^{2+}) but was made by that of high dose (0.05 mEq/kg of Ca^{2+}).

Case Report

A 28-yr-old woman was referred to the department of psychiatry presenting with substupor, mutism, mannerism, restlessness, and incoherence. She had a history of convulsion 6 months before the visit. She was initially diagnosed with hysteria. However, her laboratory data revealed the presence of hypoglycemia (33 mg/dL), and she was transferred to the division of endocrinology and metabolism for evaluation of hypoglycemia. Laboratory findings revealed no hepatic, renal, or adrenal dysfunction. Antibodies against insulin and insulin receptor were negative. She denied taking any drugs. Imaging studies, such as abdominal US, CT, MRI, and octreotide scintigraphy showed no pancreatic tumors. Fasting plasma glucose was 32–55 mg/dL. Fasting plasma immunoreactive insulin was detectable (4.4–14.9 μ U/mL). The ratios of plasma immunoreactive insulin to plasma glucose were normal (<0.3) (12).

The SACI test with the standard dose of calcium (0.025 mEq/kg) was performed as previously described (4–11). Briefly, a catheter was placed in the right hepatic vein via the right femoral vein. After catheterization of the right femoral artery, angiography of arteries feeding the pancreas was performed, which showed neither tumor stains nor abnormalities of feeding arteries. Thereafter, calcium gluconate (0.025 mEq/kg of Ca^{2+}) diluted to a 5-mL bolus was injected into superior mesenteric, splenic, gastroduodenal, and proper hepatic arteries. Blood samples were obtained from the right

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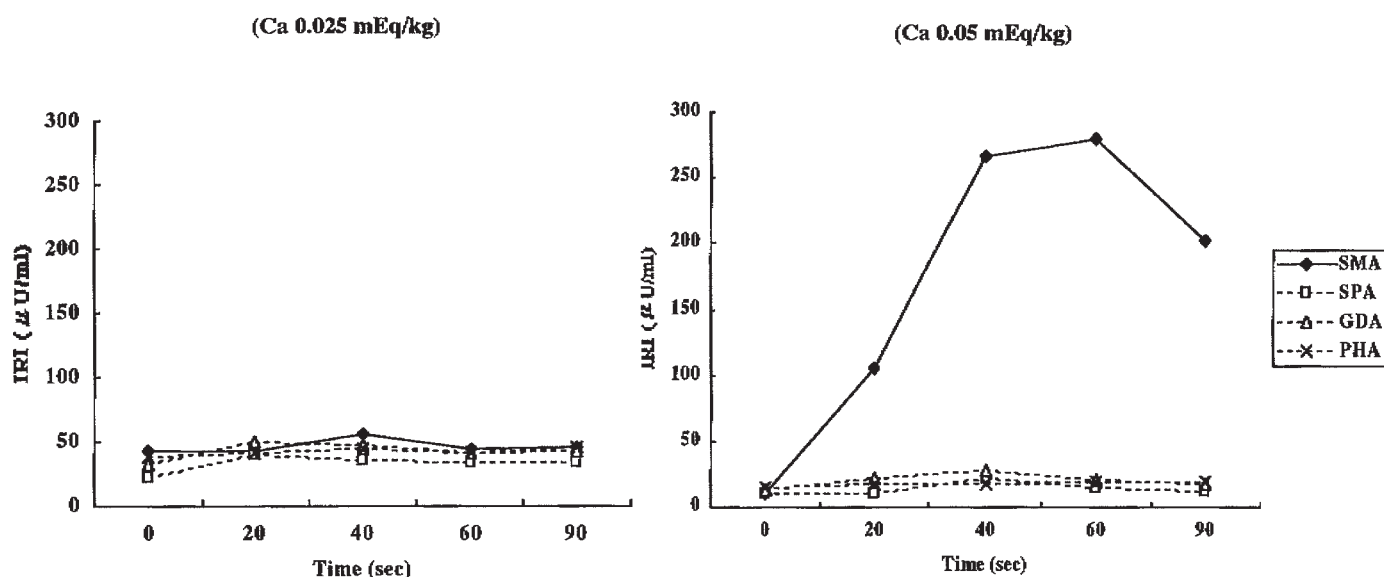


Fig 1. Results of SACI tests with 0.025 (left) and 0.05 mEq/kg of calcium (right). Significant increase in immunoreactive insulin was not seen after the second trial of SACI with 0.025 mEq/kg of Ca^{2+} (left). However, 0.05 mEq/kg of calcium injection into superior mesenteric artery increased immunoreactive insulin (right). SMA, superior mesenteric artery; SPA, splenic artery; GDA, gastroduodenal artery; PHA, proper hepatic artery; IRI, immunoreactive insulin.

hepatic vein 0, 20, 40, 60, and 90 s after the calcium injection. Plasma immunoreactive insulin concentration of each sample was measured, but it was not significantly increased at any arteries (Fig. 1, left). The SACI test was performed again, which resulted in similar data. Thereafter, the SACI test with a twofold dose of calcium (0.05 mEq/kg) was done, which demonstrated a significant increase in immunoreactive insulin (more than twofold) at the superior mesenteric artery, indicating the tumor(s) in the pancreatic head (Fig. 1, right).

At surgery, a solitary tumor (1.8 cm) was enucleated from the head of pancreas. Immunohistochemistry was performed using antiinsulin polyclonal antibody (no. N1542, guinea pig antiswine; Dako, Carpinteria, CA) and ready-to-use Envision peroxidase system (Dako) for secondary antibody. The sections were counterstained with Mayer's hematoxylin. Pathologic examinations revealed that the resected tumor was well-differentiated endocrine tumor with positive insulin immunoreactivity (Fig. 2). Postoperatively, the patient's plasma glucose was normalized, and iv injection of secretin resulted in a normal response of insulin, which was not found preoperatively. Those findings indicated that the insulinoma was completely removed (5,13) (Fig. 3).

Discussion

Patients with insulinomas often suffer from the myriad variety of neuropsychiatric disorders. Initial misdiagnosis of hypoglycemia has occurred in 20–50% of such patients (1,2). The median time interval from first hypoglycemic signs and symptoms to diagnosis ranges from 1.5 to 3 yr,

while it has taken several years to diagnose some cases of insulinomas presenting with complex neuropsychiatric disease (1–3). Furthermore, insulinomas should be included in the differential diagnosis of neuropsychiatric disorders, such as hysteria, to avoid the development of persisting neurosis, psychosis, or dementia as a consequence of chronic neuroglycopenia (3).

Surgical excision is curative in almost all cases of insulinomas, and preoperative localization is requisite for successful operation. However, abdominal US and CT detect only approx 60% of insulinomas (14,15). Relatively little has been reported about MRI in the diagnosis of insulinomas, and its exact role is uncertain (16). The sensitivity of angiography has been reported to be about 64% (17,18), while octreotide scintigraphy localizes about half of insulinomas (19). The failure of those imaging studies to detect insulinomas is attributable to the size of the tumors, which is usually <2 cm in diameter (20). Portal venous sampling can localize insulinomas in 81–100% of patients (21,22), but it requires special skills and experience and is associated with morbidity (23). The SACI test (4,5) is less invasive than the portal venous sampling and renders high predictability rates in the localization of insulinomas (4–10). The SACI test is useful especially in the diagnosis of insulinomas with normal insulin level (24,25).

Recently, a few cases of insulinomas have been reported that were not detected even by the SACI test (10,11), as in the present case. There are several possible explanations for such failure in the SACI test to localize the tumors. First, there may be anomalies of arteries feeding the pancreas. Second, the catheters may be erroneously positioned. Third,

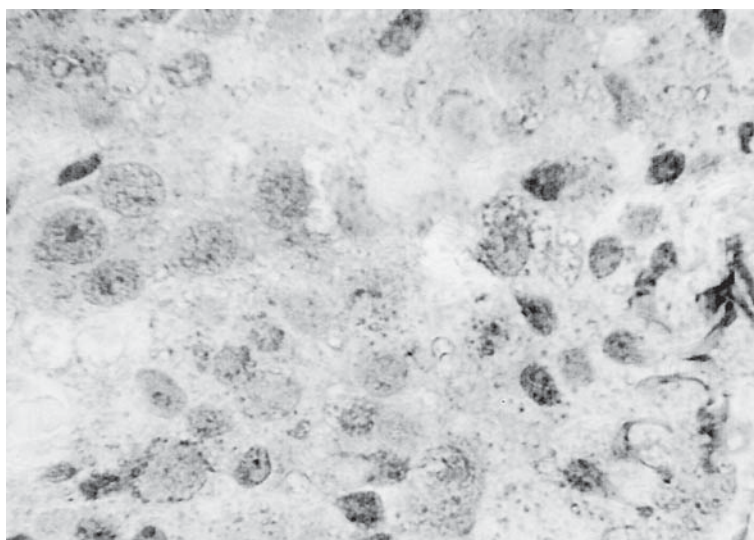


Fig 2. Immunohistochemical examination of resected pancreatic tumor specimen using antiinsulin polyclonal antibody. Precipitate represents immunoreactive insulin. Nuclei are counterstained with Mayer's hematoxylin. Insulin immunoreactivity was detected in the cytoplasm of the tumor cells (original magnification: $\times 200$)

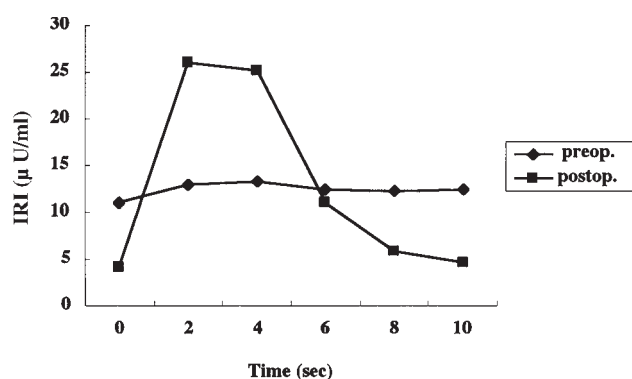


Fig 3. Results of iv secretin test before (preop) and after (postop) tumor resection. Intravenous injection of secretin (2 U/kg) increased immunoreactive insulin (IRI) postoperatively, whereas it did not preoperatively.

the injection speed of calcium may be insufficient for the stimulation of insulin release from insulinomas. Lo et al. (10) reported two cases of insulinomas located in the pancreatic body that were not detected by the SACI test, possibly owing to the relative complexity of feeding arteries to the body of the pancreas compared with its head/neck and tail. Ours is the first study using SACI with a high dose (0.05 mEq/kg) of calcium that successfully localized the insulinoma at the head of the pancreas, while that with a standard dose (0.025 mEq/kg) could not. In in vitro studies, we previously tested a variety of calcium influx mechanisms in normal B-cells and insulinoma cells and reached a conclusion that the increase in extracellular Ca^{2+} can evoke insulin release from insulinoma cells via calcium-sensing recep-

tor (26,27). We also reported that polymerase chain reaction–Southern blot analysis of human insulinoma tissues revealed the 682-bp calcium-sensing receptor cDNA; however, the expression level of calcium-sensing receptor in human insulinomas tissues was different among patients (26). Therefore, the failure to detect the tumor with a standard dose of calcium is possibly owing to the low level of receptor expression in insulinoma tissues rather than the abnormalities of feeding arteries or the catheterization errors. However, it remains to be elucidated whether other calcium-dependent mechanisms of insulin secretion, such as those via vitamin D, may be involved.

In summary, we have reported a case of insulinoma masquerading as hysteria in which only high-dose calcium injection could localize the tumor. It may be useful to perform the SACI test with a high dose of calcium in a case that is highly suspected of insulinoma if a standard dose of calcium fails to detect the tumor.

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