Insulinoma Presenting as an Unusual Cause of Marital Discord

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Months before this patient's near collapse, the metabolic derangements caused by his cancer manifested in his marriage. This case demonstrates the need to consider insulinoma in healthy appearing patients who experience behavioral disturbances that otherwise might be treated only with counseling.

Insulinomas are the most common of a rare entity—pancreatic neuroendocrine tumors. The incidence of all neuroendocrine tumors has been described as 1 to 2 per 100,000 people.[1] More than half of all neuroendocrine tumors occur in the gastrointestinal tract, with the pancreas ranking after the appendix and small bowel in site frequency.[1] Specifically, insulinomas account for four cases per million person-years,[2] and they typically present with symptoms of hypoglycemia.

Here, we present the case of an insulinoma manifesting as behavioral change that ultimately led to marital problems and an acute episode of disorientation in a young, healthy man who was subsequently found to also have a seminoma. Although we believe the two tumors to be incidental to each other, we briefly discuss our search of the medical literature for the possibility of a connection.

INITIAL EXAM

A 35-year-old, white, active duty service member was referred by his unit's physician for an endocrinology evaluation after he experienced an episode of acute disorientation. The incident occurred one day after a vigorous run. He only had eaten a light breakfast before the run and, due to his work schedule, had not eaten supper the evening before. When the patient's wife found him, he was poorly responsive and drooling. Emergency Medical Services was contacted, and they observed a capillary glucose level of 22 mg/dL. Intravenous dextrose was administered with rapid improvement in symptoms.

Upon endocrinology evaluation, the patient—who was in otherwise good health—reported experiencing moodiness and poor concentration for the past year. In fact, two months before the incident, the patient said he and his wife (a nurse) had entered counseling for marital problems. His wife had become frustrated with his increasing distractedness and unreliability for chores and declining contributions in the care of their young child. During this same time period, the patient reported experiencing sporadic episodes of fatigue, particularly after exercise. He reported smoking one cigar per week, drinking approximately one alcoholic beverage per day, and no exposure to illicit substances. He described himself as physically active and jogged and lifted weights for exercise three to five times per week.

The patient's medical history included seasonal rhinitis and sinusitis. He had no surgical history and took no prescription medications, although he reported sporadically using over-the-counter fexofenadine, pseudoephedrine, guaifenisin, ibuprofen, and acetaminophen. The patient stated that his mother and maternal grandmother had problems with low blood sugar. He was unsure of any further history, however, and denied that they had ever experienced complications or were found to have any tumors. His family history was otherwise unremarkable.

Results of physical examination and baseline laboratory studies (including complete blood count with differential, complete metabolic panel,

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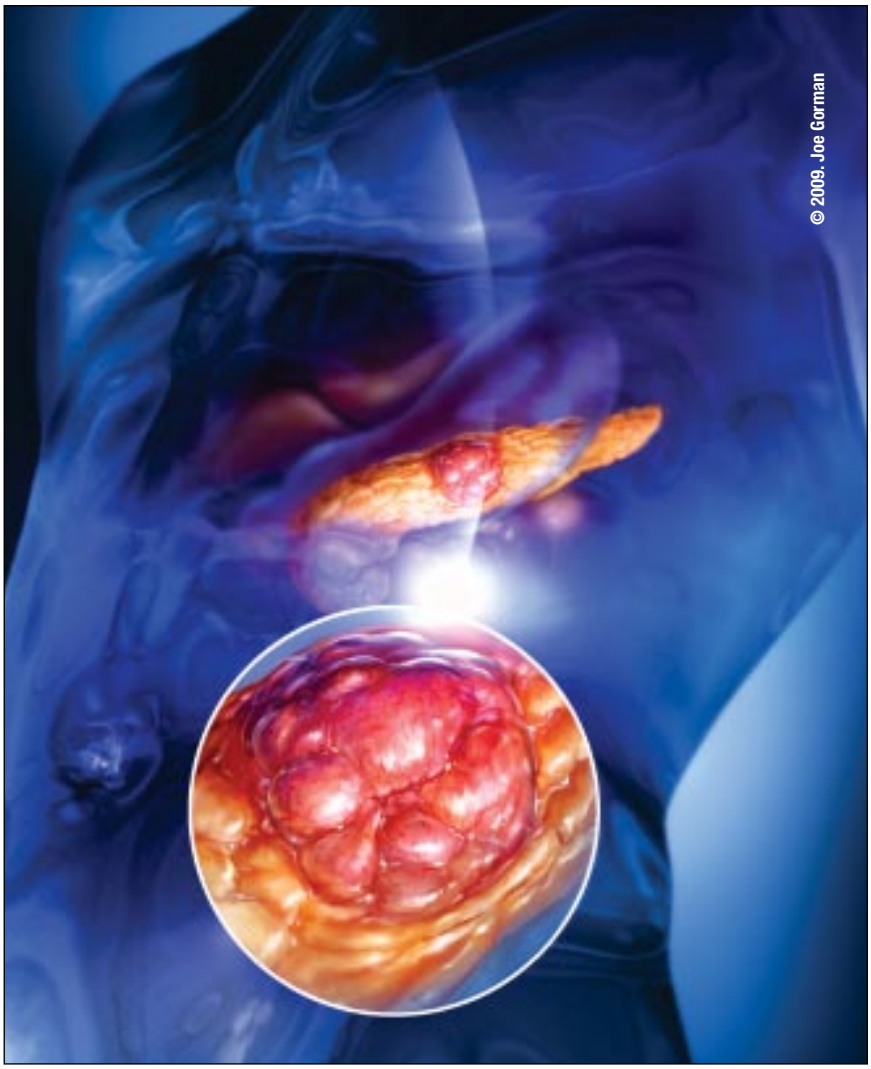
cholesterol panel, and iron studies) were normal. An adrenocorticotropin stimulation test was conducted. His baseline, 30-minute, and 60-minute serum cortisol levels were 25.4, 32.3, and 41.5 µg/dL, respectively (morning baseline reference range, 5 to 25 µg/dL). The patient was admitted for a 72-hour fast test, conducted in accordance with the Mayo Protocol.[3]

During the fast, the patient was allowed only water and underwent blood collection every four hours. He was mildly anxious throughout the test, but was able to continue with frequent reassurance. His serum glucose levels were between 30 and 45 mg/dL during the initial 40 hours of the study. Forty-one hours into the fast, the patient became somnolent. He was disoriented and answered questions with tangential sentence fragments. Additional blood collections were obtained and intravenous glucagon was administered. The patient quickly recovered. He was maintained on a dextrose in water intravenous drip for six hours and fed.

When the patient was found somnolent, his serum glucose value was 22 mg/dL—which increased to 44 mg/dL after the administration of glucagon. His serum insulin value during hypoglycemia was elevated at 28.7 µIU/mL. His serum proinsulin and C-peptide levels also were elevated at 21.3 pmol/L (reference range, 0 to 17.4 pmol/L) and 3.4 ng/mL (reference range, 0.8 to 3.1 ng/mL), respectively. Results of a urine sulfonylurea screen were negative. The patient's serum beta-OH-butyrate level was slightly elevated, however, at 0.8 mmol/L (reference range, 0 to 0.3 mmol/L).

The patient was diagnosed with endogenous hyperinsulinemia. Computed tomography (CT) scan of the abdomen revealed a 1.1-cm exophytic mass on the body of the pancreas without evidence of metastasis (Figure 1). Results of an octreotide scan were negative.



TREATMENT COURSE

Laparoscopic excision of the mass was performed. Subsequent pathology confirmed a neuroendocrine tumor consistent with insulinoma (Figure 2).

The patient did well postoperatively. He experienced normalization of his serum fasting glucose levels. His serum calcium, prolactin, and gastrin levels were normal and multiple endocrine neoplasia type 1 (MEN1) was excluded as a syndromic cause of insulinoma. He and his wife reported increased marital accord.

Two months after the diagnosis of his insulinoma, the patient identified a left testicular mass on self-examination—although a normal genital examination had been completed upon his prior endocrinology admission. He was referred to the urology department, and a local, 1.5-cm seminoma was removed. The patient continues to do well after resection of this lesion, with semi-annual follow-up in both the endocrinology and urology departments.

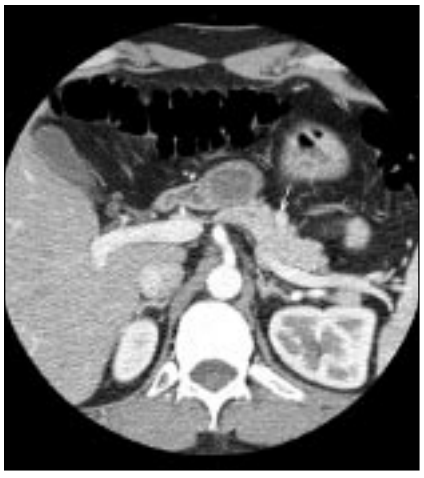


Figure 1. Computed tomography scan of the patient's abdomen showing a hyperdense, 1.1-cm exophytic mass along the pancreatic body.

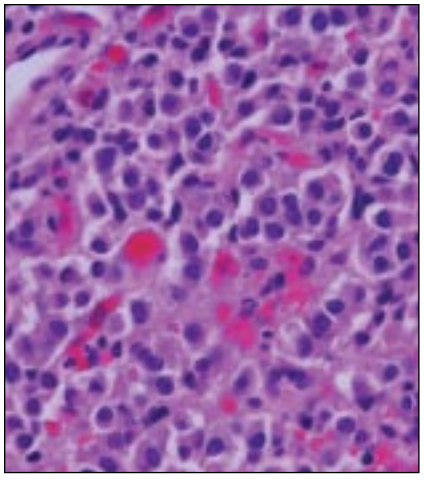


Figure 2. Histopathologic slide of the patient's neuroendocrine tumor (400 X magnification).

Table 1. Clinical classification of drug-caused hypoglycemic disorders according to appearance of patient[2]

Healthy appearing patient with no coexisting disease
- Ethanol
- Salicylates
- Quinine
- Haloperidol

Healthy appearing patient with coexisting disease
- Any drug containing sulfhydryl or thiol and autoimmune insulin syndrome
- Dispensing error
- Disopyramide
- Beta-adrenergic–blocking agents

Ill appearing patient
- Pentamadine for pneumocystis pneumonia
- Trimenthoprim-sulfamethoxazole and renal failure
- Propoxyphene and renal failure
- Quinine for cerebral malaria
- Quinidine for malaria
- Topical salicylates and renal failure

ABOUT THE CONDITION

The clinical presentation of hypoglycemia can range from symptoms of headache, nervousness, and anxiety in mild cases to seizure, coma, and death in the most severe cases. Presentation depends in part on etiology, the clinical state of the patient, and whether physiologic compensatory mechanisms are ineffective.

The differential diagnosis of hypoglycemia is broad. A clinically useful tool to guide the workup of cause for hypoglycemia—whether it be drug induced (Table 1) or brought on by a predisposing condition (Table 2)—based on the severity of the patient's presentation was proposed in 1995.[2] In addition to this guide, the author provided a diagnostic algorithm for hypoglycemia.

In the case reported here, the patient's age at onset, occupation, and social situation led to an initial differential that included factitious hypoglycemia; intense exercise coupled with poor nutrition; alcohol use; adrenal insufficiency; occult infection, such as malaria; and insulinoma. We diagnosed endogenous hyperinsulinemia as the etiology for the patient's hypoglycemia given the presence of elevated serum insulin and C-peptide levels and the absence of sulfonylurea in the patient's urine.

Insulinomas occur in isolation or, about 7% to 8% of the time, as part of a syndrome.[3] Less commonly they occur as tuberous sclerosis or von Hippel-Lindau syndrome.

Our patient presented with neuroglycopenia. This metabolic abnormality may manifest as personality or behavioral change, confusion, cognitive decline, vision changes, amnesia, seizures, or coma.[3,4] The patient's history of distractedness and family tension, as well as the anxiety he displayed, may represent his compensatory counter-regulatory hormone surge and history of subclinical and transient hypoglycemic episodes. Fortunately, our patient had a sporadic, solitary lesion amenable to resection by video laparoscopy.

The optimal approach to treatment, even in the setting of multiple metastatic lesions, is considered to be localization by CT scan followed by surgical resection. If the tumor is

Table 2. Clinical classification of predisposing condition–caused hypoglycemic disorders according to appearance of patient[2]

Healthy appearing patient with no coexisting disease
- Insulinoma
- Factitious hypoglycemia induced by insulin
- Intense exercise
- Ketotic hypoglycemia

Healthy appearing patient with coexisting disease
- Ackee-fruit poisoning and undernutrition

Ill appearing patient
- Small size for gestational age in infants
- Backwith-Wiedemann syndrome
- Erythroblastosis fetalis
- Hyperinsulinemia in infants due to maternal diabetes
- Glycogan storage disease
- Defects in amino acid and fatty acid metabolism
- Reye syndrome
- Cyanotic congenital heart disease
- Hypopituitarism
- Isolated growth hormone deficiency
- Isolated corticotropin deficiency
- Addison disease
- Galactosemia
- Hereditary fructose intolerance
- Carnitine deficiency
- Defective type 1 glucose transporter in the brain
- Acquired severe liver disease
- Large non–beta-cell tumor
- Sepsis
- Renal failure
- Congestive heart failure
- Lactic acidosis
- Starvation
- Anorexia nervosa
- Surgical removal of phaochromocytoma
- Insulin-antibody hypoglycemia

Hospitalized patient
- Hospitalization for a predisposing illness
- Total parenteral nutrition and insulin therapy
- Interference of cholestyramine with glucocorticoid absorption
- Shock

not localized by preoperative imaging, intraoperative ultrasound can be utilized along with calcium infusion and stimulation if indicated.

An insulinoma-seminoma connection?

A Medline search revealed no literature with a clear link of insulinoma with seminoma, and we believe that ours is the first documented case of these tumors coexisting in a patient. One study described the occurrence of these tumors in five-week-old rats exposed to radiation but none of the rats were reported to develop both insulinoma and seminoma.[5] Our patient had no known history of prior irradiation; therefore, the coexistence of these tumors was likely coincidental. While our patient showed no signs of tuberous sclerosis or von Hippel-Lindau syndrome, there may be links between these disorders and testicular tumors. Leydig cell tumors and testicular interstitial neuroendocrine tumors are sometimes grouped with pancreatic tumors in animal studies and may be related, but there is no known link between seminoma and insulinoma. We found a single case report that cites Leydig cell tumor in a patient with tuberous sclerosis.[6] While it has been postulated that the trophic effect of insulin or insulin-like growth factor may have a role in the development of germ cell tumors, one observational study demonstrated an inverse relationship between the concentration of insulin-like growth factor and the risk of germ cell tumor.[7] Overall, insufficient evidence exists to associate insulinomas with seminomatous testicular cancer.

IN CONCLUSION

While rare, insulinomas are discoverable and treatable. Since clinical hypoglycemia declares itself with a wide range of neurobehavioral signs and symptoms, changes in behavior in a given patient can lead to the identification of metabolic derangement. This case, in particular, demonstrates the need to consider metabolic derangements in patients who experience behavioral disturbances that are initially treated with counseling. When evaluating for hypoglycemia,

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a 72-hour fast is a useful diagnostic intervention when indicated.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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