CLINICAL VIGNETTE

Challenges of Diagnosing and Treating Insulinoma in Patients with Co-Morbidities

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Case Presentation

A 72-year-old female with recurrent falls with hip fracture, deep vein thrombosis/pulmonary embolism presented to a tertiary care hospital for treatment of DVTs. She had hypoglycemic episodes during her hospitalization and endocrinology was consulted.

The patient had intermittent glucose measurements below 55 mg/dL requiring intravenous D50 treatment. She had mild cognitive deficits noted during her prolonged hospitalizations. While malnutrition was suspected as a possible cause of hypoglycemia, a 72-hour fast was performed to further evaluate her hypoglycemia. The 72-hour fast ended after 36-hours when the patient developed hypoglycemia with glucose level of 42 mg/dL with concomitantly elevated serum C-peptide, Insulin and pro-insulin (see Table 1). This confirmed hyperinsulinemic hypoglycemia and suggested an insulinoma. CT abdomen did not show any pancreatic tumor. Further evaluation including endoscopic ultrasound as well as surgical explorations was declined, however, due to her co-morbidity the patient's family declined pursuing further work up or surgical treatment. Diazoxide was considered as first line treatment of hypoglycemia but was not used due to pre-existing lower extremity edema due to history of DVTs. Octreotide was initiated instead, and the patient's hypoglycemia episodes resolved prior to her discharge. She was discharged to skilled nursing facility on octreotide with the recommendation to follow up in endocrine clinic.

Five years later, at the age of 77 years old, she was admitted to a different hospital for evaluation of chronic loose stool as well as gradually worsening confusion and weakness. MRI of the abdomen on admission showed a 1.5cm pancreatic mass (Figure 1). She was noted to have hypoglycemia (48mg/dL, 51mg/dL) that did not resolve with initiation of intravenous D10 infusion or initiation of diet. The endocrinology service was consulted. Per the patient's family, her cognitive deficit has gradually worsened over the past few years to the point that they contemplated hospice care for dementia. In the 6 months prior to admission, she experienced more frequent falls, loss of balance, along with weight loss of 30 lbs. Her symptoms seemed to improve after she ate. The patient and family had forgotten about her hypoglycemia diagnosis from 5 years prior. They had not been monitoring her glucose nor administering octreotide at home. On exam, the patient was alert and had clear speech but had difficulty with memory. The patient's family denied noticing a difference in her cognitive function when her glucose was 40 mg/dL compared to when it improved to 100 mg/dL after D50. She was largely asymptomatic during hospitalization even when glucose level was as low as 40 mg/dL, without sweating, tachycardia, palpitation, lightheadedness or tremors.

Table 1. Laboratory testing results from 72-hour fast and other hypoglycemia work up

72-hour fast data (completed at 36 hours after start of fast)	Other hypoglycemia work-up
Serum glucose 42 mg/dL C-peptide 2.8 ng/dL (normal <0.02) Insulin 16 uUUL (normal <3) Pro-insulin 8.1 pmol/L (normal <5) Beta hydroxybutyrate 1.9mg/dL (expected to be low in hyperinsulinemic state) After glucagon administration, glucose increased to 77mg/dL	Insulin Ab <0.4 (negative) Insulin-like growth factor 402 (normal) Sulfonylurea screen -negative

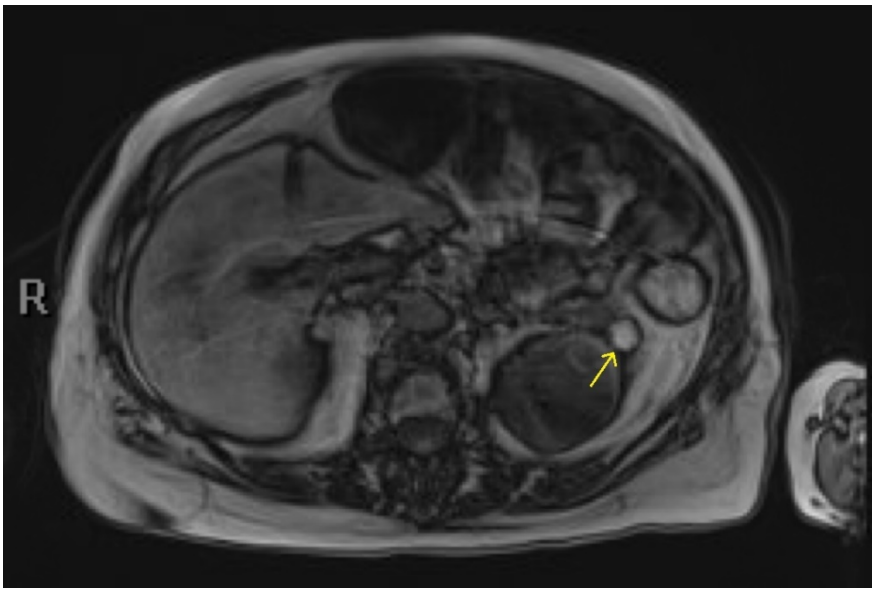

Figure 1. MRI Abdomen with/without contrast (1.5cm tumor noted in distal pancreas)

Adrenal insufficiency was ruled out as cause of hypoglycemia with normal serum cortisol level. Given her previous 72-hour fast results, the pancreatic mass was suspected to be an insulinoma. Surgical and medical treatment options were discussed. The patient and family initially didn't want to consider surgery due to her co-morbidity. Octreotide 100mcg subcutaneous injection was given every 8 hours during admission which controlled her hypoglycemia. Ultimately, the patient underwent distal pancreatectomy and splenectomy due to concern for malignancy, surgical pathology confirmed a 1.7cm well differentiated neuroendocrine tumor in pancreatic tail with negative margin and negative lymph nodes, suggesting benign pathology. She didn't have any further hypoglycemic episodes during the rest of the hospital stay or after discharge.

Discussion

Insulinoma is a rare disease, with reported incidence of 4 cases per million person-years.[1] However, it is the most common cause of endogenous hyperinsulinemic hypoglycemia in people without diabetes.

Hypoglycemia is defined with Whipple's triad: hypoglycemia with glucose <55 mg/dL, symptoms consistent with hypoglycemia and improvement of symptoms after restoration of glucose to normal range with glucose administration.[2] Diagnosing insulinoma is often difficult in the outpatient setting as it requires the patient to have labs done at the time of hypoglycemia which carries significant safety concerns. Many patients require hospital admission to complete a 72-hour fast test, which is the gold standard for diagnosis of hypoglycemia. When biochemical diagnostic test confirms hyperinsulinemic hypoglycemia in a patient without diabetes, with negative secondary work up of hypoglycemia, index suspicion of insulinoma should be very high.

The diagnosis of insulinoma is even more challenging in elderly patients and patients with multiple co-morbidities as they have reduced adrenergic response to hypoglycemia.[3,4] Additionally, frequent hypoglycemia episodes have been associated with dementia in elderly patients,[5] and elderly patients with underlying cognitive deficit may not show acute improvement of cognition when hypoglycemia improves. This may delay diagnosis of insulinoma as neuroglycopenic symptoms of confusion in elderly can be misdiagnosed as dementia.[6] As a result, elderly patients may present with atypical symptoms, such as fall, syncope, cognitive decline[3,6,7] or may be found to have hypoglycemia incidentally on lab testing. A 60-year observational study reported median duration of symptoms of 1.5 years before diagnosis of insulinoma.[1] Some patients may have been symptomatic for a decade prior to diagnosis. Our patient reported having multiple falls, cognitive decline for many years and possibly had undiagnosed hypoglycemia for many years prior to her diagnosis.

Abdominal CT or MRI are the initial imaging study of choice for localization of insulinomas and they are able to detect 72-75% of tumors pre-operatively and, rule out metastasis for unresectable tumors.[8] However, up to 30% of insulinomas may be smaller than 1 centimeter[2] and may not be visible on these imaging modalities. When suspicion of insulinoma is high, more aggressive diagnostic testing for tumor localizations is indicated, including endoscopic ultrasound (EUS), selective arterial calcium stimulation with hepatic venous sampling or even surgical exploration. Surgery is the recommended treatment of choice when possible as many patients can achieve cure when the tumor is completely resected. Experienced medical centers may offer ethanol ablation of insulinoma for patients with high surgical risk.[9] For patients who decline diagnostic studies or surgical intervention, who are not candidate for surgery due to comorbidities or unresectable disease, and who have recurrence of hypoglycemia after surgery, medical treatment to control hypoglycemia is indicated. Delaying treatment

of insulinoma carries high morbidity and mortality from unpredictable hypoglycemia. Medical treatment options include Diazoxide which is an antihypoglycemic drug that acts as a potassium channel opener on *b*-pancreatic islet cells, resulting in decreased insulin secretion. The use of Diazoxide can be limited by its availability or its side effect of edema. Octreotide and Lanreotide are somatostatin analogs and have been used for persistent hypoglycemia that is refractory to diazoxide.[2,7] Octreotide is given as an every 8 hour subcutaneous injection. Alternatively, the depo version of Lanreotide can be given as a monthly injection in clinic to improve compliance.

Although 90-95% of insulinomas are benign, malignant insulinomas usually metastasize to the liver and lymph nodes.[1,2,10] In our patient, the pancreatic mass grew over 5 years without liver metastasis on imaging. However, marked weight loss led to surgical resection.

This case illustrates the difficulty of diagnosis and management of insulinoma in elderly patients with co-morbidities. The patient's chronic cognitive deficit and lack of classic adrenergic hypoglycemic symptoms led to delayed diagnosis of insulinoma which resulted in significant morbidity. Physicians should evaluate unexplained hypoglycemia in elderly patients even if they are asymptomatic, as misdiagnosis or delayed diagnosis and treatment of insulinoma carries high morbidity and mortality. When a patient without diabetes experiences recurrent hypoglycemia, insulinoma should be considered as the top differential diagnosis even when imaging study does not show any pancreatic tumor.

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