Case Report

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Recurrent Syncope, Behavioral Changes and Weight Gain in an Elderly Filipino Woman: Successful Diagnosis and Management of Insulinoma With 13-Year Disease-Free Follow-up

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Abstract

Recurrent syncope and behavioral changes in the older population may suggest several disease entities associated with aging. Hypoglycemia is an often-missed potentially correctable underlying cause that should also be considered in the differential diagnosis. We present a case of a 62-year-old Filipino woman who presented with recurrent syncopal attacks, behavioral changes and unintentional weight gain, associated with endogenous hyperinsulinemic hypoglycemia with no pancreatic mass seen on abdominal CT scan. A pancreatic head tumor was visualized through endoscopic ultrasound. Surgical removal of the mass resulted in resolution of her symptoms and restoration of her physical and functional well-being. This case is being reported to highlight that surgery cured her of the disease and she remains asymptomatic and well 13 years after her surgery.

Key words: hypoglycemia, insulinoma, pancreatic neoplasms, weight gain, syncope, blood glucose

INTRODUCTION

Recurrent syncope and behavioral changes in the older population may suggest several disease entities associated with aging. The most common of which are cerebrovascular diseases, complex seizures, Alzheimer's disease, and psychiatric illnesses among others. However, metabolic disorders which are potentially correctible underlying causes should also be considered in the differential diagnosis. Non-visualization of a pancreatic tumor on routine imaging should not deter the physician from doing extensive evaluation of a patient with high index of clinical suspicion. Definitive management of insulinoma may significantly improve the quality of life of the patient.

CASE

Recurrent syncope and behavioral changes in the older population may suggest several disease entities associated with aging. The most common of which are cerebrovascular diseases, complex seizures, Alzheimer's disease, and psychiatric illnesses. However, metabolic disorders which are potentially correctible underlying causes should also be considered in the differential diagnosis. Non-visualization of a pancreatic tumor on routine imaging should not deter the physician from doing extensive evaluation of a patient with high index of clinical suspicion. Definitive management of insulinoma may significantly improve the quality of life of the patient.

Clinical presentation

A 62-year-old Filipino woman presented with light-headedness which later progressed to unresponsiveness. She had a history of recurrent dizziness for 5 years, relieved with food intake. It was associated with episodes of behavioral changes described as blank stares, inability to recognize family members, and repetitive washing or folding of clothes.

She had 3 similar episodes for the past 5 years all associated with low capillary blood glucose (CBG) (lowest level was 1.5 mmol/L), responsive to intravenous glucose infusion. Subsequent investigation done 3 months ago showed a low CBG at 1.5 mmol/L (normal range, 4.0-5.5 mmol/L), an insulin level of 41.8 IU/ml [normal value (NV) 0-23] and a C-peptide level of 5.282 ng/ml (NV 1.07-3.51). An upper abdominal CT did not reveal any pancreatic mass. There was an incidental finding of a 1.4 cm left renal cortical cyst. Plain computed tomography (CT) of the brain did not show mass any lesion or infarct.

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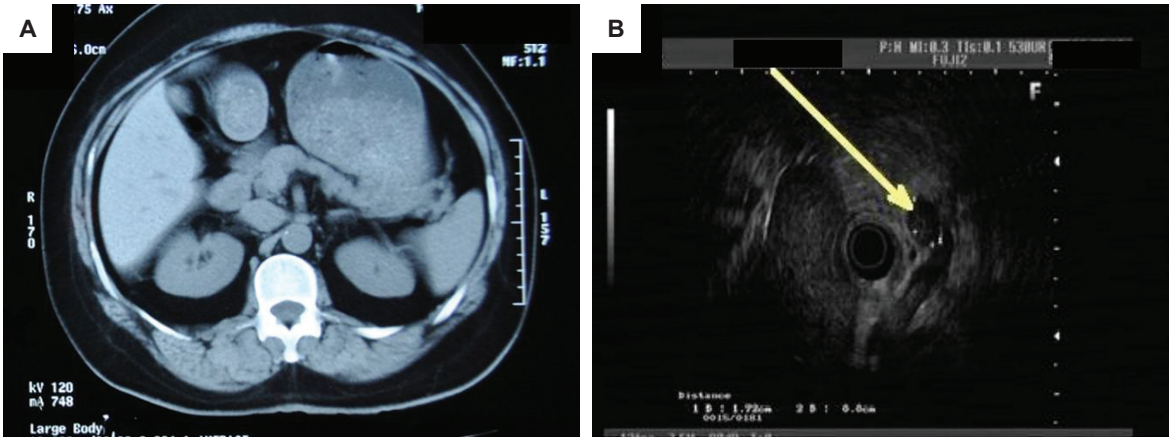

Figure 1. (A) Plain abdominal CT scan did not reveal pancreatic mass. **(B)** Endoscopic ultrasound showing a pancreatic head tumor *(yellow arrow)*.

She noticed an increase in appetite for the past few years leading to weight gain. However, she denied having headaches, blurring of vision, galactorrhea, heat or cold intolerance, or hyperpigmentation which may suggest pituitary disease. There was no history of fractures or nephrolithiasis which may suggest hyperparathyroidism. She had been hypertensive for the past 3 years, taking imidapril + hydrochlorothiazide. Medication history revealed intake of vitamin B complex and occasional use of herbal supplement (mangosteen extract). She denied insulin use or intake of oral hypoglycemic agents (OHA). All her previous hospitalizations were due to hypoglycemia.

On physical examination, she was lethargic but with normal vital signs. She was obese with a body mass index (BMI) of 30.5 kg/m^2. The rest of the physical findings were unremarkable. Neurologic evaluation revealed scanning speech, nystagmus, shallow left nasolabial fold, limb ataxia, positive Romberg's sign, and bilateral Babinski sign. The CBG on admission was 1.8 mmol/L which increased to 7.4 mmol/L after intravenous administration of 25 grams glucose solution.

Investigations

The admitting diagnosis was endogenous hyperinsulinemic hypoglycemia, recurrent and symptomatic (syncopal attacks) most probably from insulinoma, not visualized on abdominal CT scan.

Her laboratory work-up showed a very low fasting blood sugar (FBS) at 0.25 mmol/L, an elevated creatinine level of 162 umol/L (creatinine clearance of 34 mL/min), normal calcium at 2.31 mmol/L (NV 2.15 - 2.5) and a serum cortisol at 331.08 nmol/L (NV 160-620). Thyroid-stimulating hormone was also normal at 0.9 mIU/L (NV 0.3–3.8). Since a plain abdominal CT scan done in a previous hospital did not show any pancreatic mass, an endoscopic ultrasound (EUS) was pursued instead of doing a repeat CT with intravenous contrast. EUS showed a 1.7 x 1.3 cm, hypoechoic, heterogenous, round pancreatic head mass abutting the splenic vein, with normal pancreatic duct, bile duct and other visualized areas of the liver. The impression was a pancreatic head mass, to consider a neuroendocrine tumor (Figure 1). She was then scheduled for enucleation.

Neurology referral was also done for dysarthria and other neurologic findings. A posterior circulation ischemia of the left ponto-cerebellar area was considered. A cranial CT scan was done to rule out stroke and other space-occupying lesions. Results showed microvascular ischemic changes, cerebro-cerebellar atrophy with ex-vacuo ventricular dilatation. There was no sellar-suprasellar mass noted. A 21-channel electroencephalogram (EEG) showed mild diffuse slowing of the background activity indicative of mild diffuse cerebral dysfunction of no specific etiology. An MRI of the brain was not anymore pursued since the shallow left nasolabial fold, which was the lone lateralizing sign the patient manifested with, eventually resolved after normalization of blood glucose levels.

Differential diagnosis

Diseases which could also present with recurrent syncopal attacks and behavioral changes include psychiatric disorders, complex seizures, vascular dementias or cerebrovascular disease. Possible causes of hypoglycemia are surrep-titious insulin or OHA use, nesidioblastosis, or presence of anti-insulin antibody. Multiple endocrine neoplasia 1 (MEN-1) may also be considered.

Normal psychiatric evaluation coupled with the absence of a mass lesion on cranial CT scan and diffuse slowing of background activity on EEG ruled out psychiatric and neurological disorders in this case. Extensive medical history and drug intake history made the surreptitious drug use less likely. A high C-peptide level of the patient is also not consistent with surreptitious insulin use. Nesidioblastosis or diffuse hyperplasia of the islets was also considered due to the initial non-visualization of the pancreatic mass on abdominal CT scan. However, most cases start during infancy and childhood, predominantly in males and

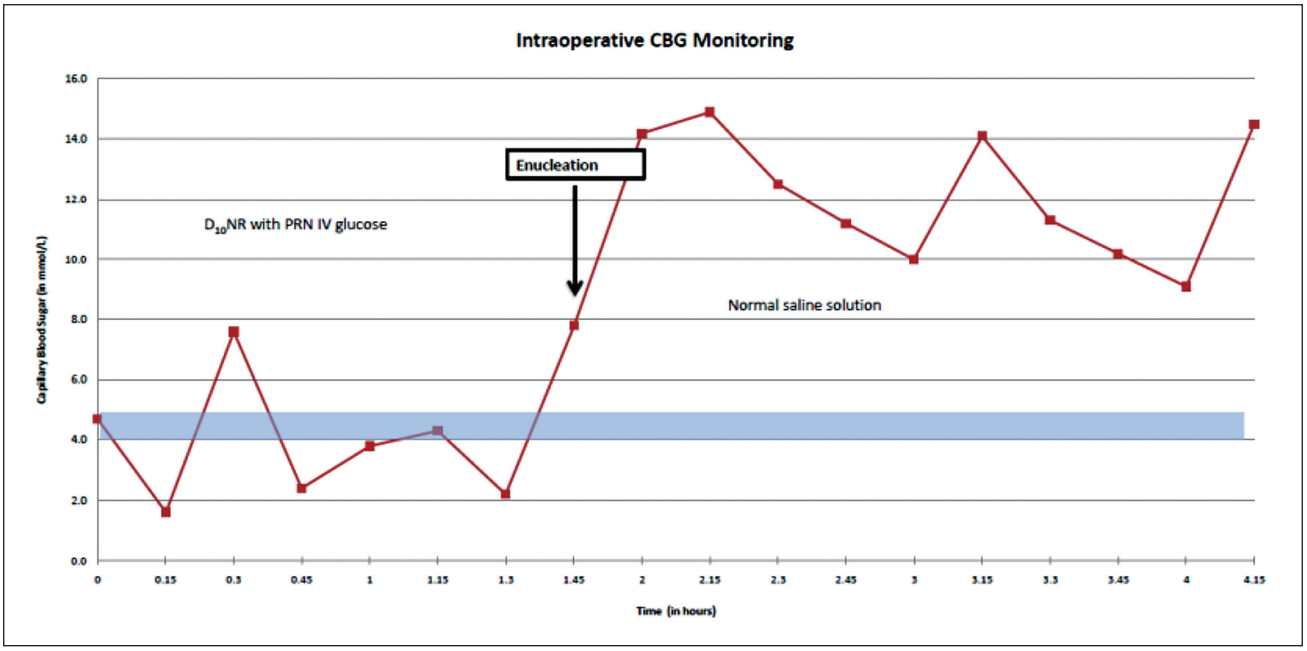

Figure 2. Intraoperative capillary blood glucose monitoring. Note the immediate rise in blood glucose levels post-enucleation of the pancreatic head tumor *(arrow signifies the time when the mass was removed)*. The blue bar represents the normal range of capillary blood glucose.

the episodes of hypoglycemia usually occur during the postprandial state. Hypoglycemia due to the development of native insulin antibodies is usually observed in the late postprandial period and is seen frequently in patients with history of autoimmune disease or exposure to sulfhydryl-containing drugs, which were not observed in this patient. MEN-1 was ruled out on the basis of the absence of pituitary involvement or parathyroid involvement as suggested by the normal cranial CT scan and normal serum calcium levels. However, this patient may have some degree of adrenal insufficiency based on the mid-normal serum cortisol levels in the setting of hypoglycemia, which is an inappropriate response. The expected response is an increased level of serum cortisol, being a counterregulatory hormone for hypoglycemia.

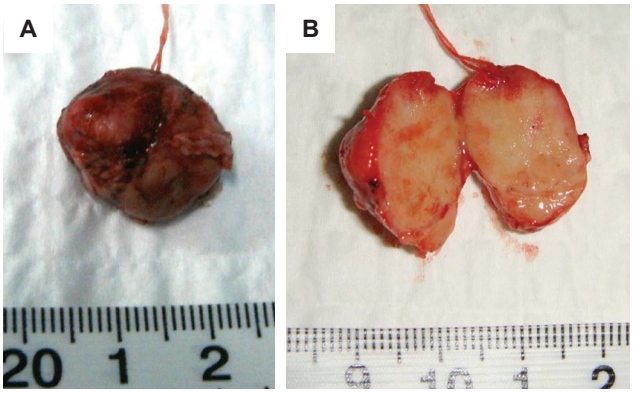

Figure 3. (A) Gross appearance of the 2-cm pancreatic head mass post-enucleation. **(B)** Cross-section of the mass.

Treatment

Enucleation of the pancreatic head mass after intraoperative ultrasound and palpation was done showing a 2 cm well-circumscribed, encapsulated pancreatic head tumor.

Upon enucleation of the tumor, CBGs immediately increased and values ranged between 8.9–14.4 mmol/L. Post-operatively, there was no episode of hypoglycemia noted (Figure 2).

Figure 3 shows the gross and cut section appearance of the tumor. Histopathology showed uniform cells in anastomosing cords consistent with an islet-cell tumor of the pancreas (pancreatic neuroendocrine tumor) (Figure 4). Immunohistochemical staining was positive for chromogranin A and synaptophysin proving the neuro-endocrine nature of the tumor (Figure 5). Insulin immuno-stain was contemplated but could not be done due to unavailability in the country.

Post-operatively, she developed acute pancreatitis, sepsis, acute kidney injury from ischemic acute tubular necrosis, and delirium. Careful hydration, imipenem, and other supportive treatment were given. She gradually improved in the subsequent days. There was no recurrence of syncope, behavioral changes or hypoglycemia. Her renal function improved. She was discharged on the 25th hospital day.

Outcome and follow-up

There were no episodes of behavioral or sensorial changes noted at home. Preprandial capillary blood sugars ranged from 6.1 – 7.2 mmol/L. The patient was consistently coherent and was able to resume her usual daily activities without assistance. On outpatient follow-up, she was comfortable,

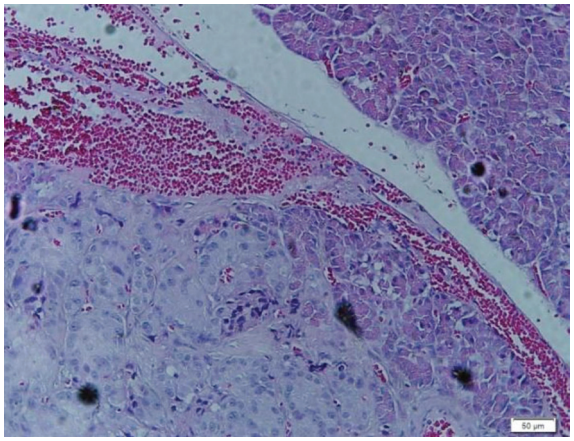

Figure 4. Normal pancreatic tissue on the right upper portion, with the pancreatic head mass (islet cell tumor / pancreatic neuroendocrine tumor) at the lower left side of the photomicrograph appearing as uniform cells in anastomosing cords (H&E, 40x).

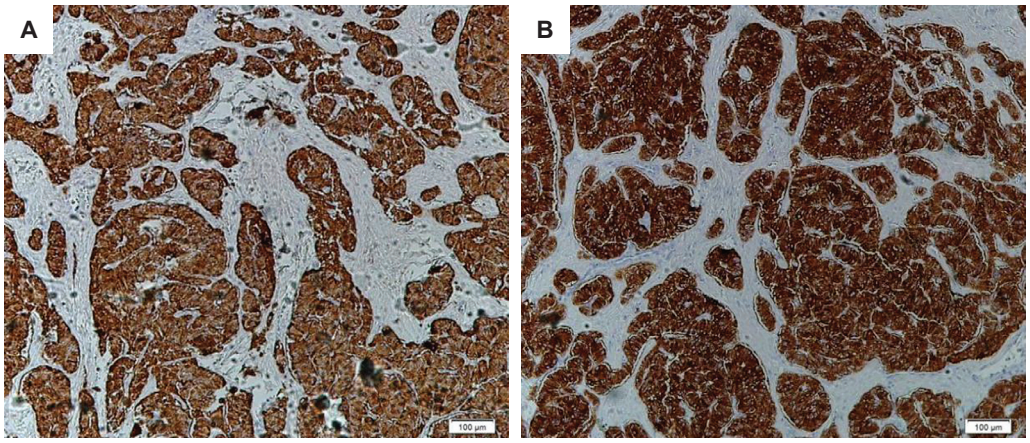

Figure 5. Positive chromogranin **(A)** and synaptophysin **(B)** immunohistochemical staining of the pancreatic head mass, 100x magnification.

generally felt better and had a positive outlook in life. Her BMI decreased from 30.5 kg/m^2 to 24 kg/m^2 two months after the surgery (Figure 6).

Thirteen years after surgery, there has still been no recurrence of hypoglycemic symptoms and she remains functionally independent at age 75. She weighs 42 kg with a BMI of 18.1 kg/m^2. Screening for fracture risk using FRAX Plus revealed a 10-year probability for major osteoporotic fractures of 4.3% and for hip fractures of 2.3%. These are above the therapeutic thresholds for Filipinos, hence anti-osteoporosis medications were recommended. She remains independent in all activities of daily living and is not frail using the Edmonton Frail Scale. She has yet to be screened for diabetes.

DISCUSSION

Insulinoma is a very rare disorder with an incidence rate of 4 per 1,000,000 persons. Among the endocrine pancreatic tumors, it is the most common functional neuroendocrine pancreatic neoplasm accounting for 70 to 80 percent.[1] The median age is estimated at 47 years (age range 30 – 70 years), with slight female predominance (59%). Insulinomas are usually solitary, benign and sporadic, 90% are less than 2 cm, 30% are less than 1 cm, 10% are multiple,

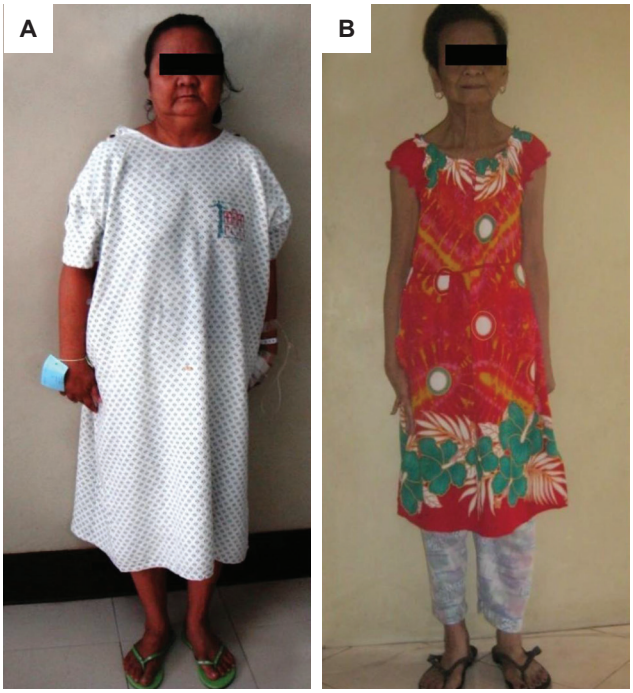

Figure 6. Photograph of the patient before surgery **(A)** with a BMI of 30.5 kg/m^2 and 2 months post-operatively **(B)** with a BMI of 24 kg/m^2.

10% are malignant, and 16% are associated with multiple endocrine neoplasia 1 (MEN-1).[1,2] The hypoglycemic symptoms are classified as either neuroglycopenic or adrenergic.[3] Neuroglycopenic symptoms include altered mental status, visual disturbance, amnesia/coma, abnormal behavior, and seizures. Adrenergic symptoms include sweating, weakness, obesity, tremors, hyperphagia, and palpitations. Symptoms that were present in our patient were altered mental status, abnormal behavior, obesity, and hyperphagia.

In the stepwise approach for the diagnosis of insulinoma, it is recommended to first confirm the hypoglycemia, followed by documentation of hyperinsulinism, differentiating endogenous from exogenous sources. Thereafter, localization studies of the tumor are performed, and appropriate treatment are done based on the diagnostic results.[4]

Localization studies include both non-invasive and invasive modalities. Non-invasive procedures include transabdominal ultrasonography, abdominal CT scan or MRI. Invasive procedures are employed only upon high suspicion for insulinoma and failure of all non-invasive imaging tests to detect the lesion. Among these are selective pancreatic arteriography, transhepatic portal venous sampling, intra-arterial calcium stimulation with hepatic vein catheterization, endoscopic ultrasound (EUS), and intraoperative ultrasonography. Newer modalities for localization are somatostatin receptor scintigraphy and GLP-1 receptor scintigraphy.[5,6]

What was initially done on this patient was an abdominal CT which was negative. The tumor was eventually localized using an EUS which showed a 1.7 x 1.3 cm tumor in the pancreatic head. Intraoperative ultrasound confirmed the presence of a 2-cm well-circumscribed, encapsulated pancreatic tumor.

After localization, our patient underwent tumor enucleation. Tumor enucleation is the procedure of choice for solitary benign tumors that are located in the pancreatic head. Those unsuitable for enucleation may have segmental resection of the pancreas, distal pancreatectomy, pancreaticoduodenectomy and formal resection for those suspicious for malignancy. Post-operative complications include pancreatic fistula, pseudocyst, intraabdominal abscess, pancreatitis, hemorrhage and diabetes.[5] According to a systematic review and meta-analysis, enucleation is a safe procedure, with a postoperative mortality of 1.1%, tumor recurrence rate of 3.1%, and acute pancreatitis occurrence rate of 1.7%.[7] Post-operative pancreatitis was observed in our patient.

Morbidity rate ranges from 10–43%, mortality rate at 0-4% and surgical cure rate was reported at 89-96%.[5] A multicenter study in Turkiye determined the remission rate at 91%.[8] Medical management may be done in those unsuitable for surgery, those awaiting surgery, those with unresectable disease, and those with unsuccessful operation. Dietary modification has a goal to prevent prolonged periods of fasting. Drugs used in the medical management include diazoxide, octreotide acetate, verapamil, propranolol, phenytoin, everolimus and sunitinib malate.[5] Our patient improved significantly with surgical management alone.

A study in Finland showed that the overall survival of non-metastatic insulinoma treated with curative-intent surgery was similar to controls.[9] Hence, our patient can expect normal life expectancy similar to control individuals, now that she has undergone enucleation.

This case has learning value for the following reasons. First, there are many causes of behavioral changes among senior citizens and hypoglycemia is not among the common ones. This teaches us to always check blood glucose levels in those with acute behavioral changes. Performing point-of-care capillary blood glucose determination is a rapid test that will make a primary care or emergency physician refer cases similar to this first to an internist-endocrinologist rather than to a neurologist.

Second, it is generally believed that metabolic causes of encephalopathy would not present with localizing neurologic deficits. Our patient had a shallow left nasolabial fold which would suggest a right frontal lobe lesion. Cranial CT scan, however, did not show a focal lesion. This, plus the resolution of the neurologic deficits upon correction of hypoglycemia, means that metabolic causes can cause transient "localizing" deficits.

Third, weight gain was very prominent in this case such that the patient was happy that she lost weight in as short as 2 months after surgery. Unintentional weight loss, which is part of frailty, is usually a problem in the elderly. However, what she had was the opposite and this makes it an unusual symptom in her age group.

Fourth, the absence of a pancreatic mass on CT scan should not make doctors easily exclude an insulinoma. In this case, we had to perform endoscopic ultrasound to localize the lesion preoperatively. Admittedly, this is a technology that may not be available in all medical centers in our country and the expertise of a gastroenterologist in doing this procedure is also uncommon.

Fifth, this case shows that management of an insulinoma requires multidisciplinary teamwork. Physicians in the field of endocrinology, pancreatic surgery and gastroenterology had to work together to achieve a favorable outcome for this patient.

Sixth, the long duration of follow up is one of this case's strength. The fact that she remains disease-free up to 13 years after surgery supports the knowledge that surgery can be curative. This can help physicians convince other similarly situated patients to undergo surgery so they can look forward to a cure and near-normal life expectancy.

Learning Points

- Insulinoma, though a very rare yet potentially reversible disorder, should be considered in the differential diagnosis of elderly patients presenting with recurrent syncope, behavioral changes and weight gain.
- Non-visualization of pancreatic mass on routine imaging should not prevent the physician from pursuing the diagnosis of insulinoma in those patients with high index of clinical suspicion.
- Surgical enucleation of a solitary insulinoma has a high cure rate and may dramatically improve the metabolic status of the patient and his/her overall physical and functional well-being.
- Curative surgery can lead to disease-free survival for up to 13 years and counting.

Ethical Consideration

Patient consent forms were obtained before manuscript submission.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

EC: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Visualization; **MAS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – review and editing, Visualization, Supervision.

Data Availability Statement

No datasets were generated or analyzed for this study.

Author Disclosure

Both authors declared no conflict of interest.

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None.

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