

Insulinoma Diagnosed with Endoscopic Ultrasound – Two Cases

by Brijesh B. Patel, Thure Caire, Prasad Kulkarni

We present two cases of insulinoma diagnosed by endoscopic ultrasound (EUS) after initial imaging was unrevealing. Both patients presented with refractory hypoglycemia and were found to have high c-peptide and insulin levels suspicious for insulinoma with evaluation for factitious causes (sulfonylurea, and meglitinides screening) being ruled out. However, imaging with computed tomography (CT) or magnetic resonance imaging (MRI) was not revealing of lesion location. Subsequently, EUS was pursued. In each case, EUS was able to localize and biopsy the lesion in the head of the pancreas and immunohistochemistry confirmed the diagnosis. Both patients underwent definitive treatment and had uneventful recovery. These cases highlight the utility of EUS in diagnosing and localizing insulinoma.

INTRODUCTION

Insulinomas are rare neuroendocrine tumors (NET) with an annual incidence ranging from 1 to 4 people per million per year. Although rare, they are the most common of the NETs, with a higher female predominance and typical presentation in the 5th decade of life.¹ Only 5-10% of insulinomas are malignant. After gastrinoma, insulinoma is the second most common functioning pancreatic tumor, accounting for 10-30% and are associated with multiple endocrine neoplasia (MEN type 1).² They are usually small in size < 2 cm.³

The clinical presentation of insulinoma may include diaphoresis, tremor, palpitations and uncharacteristic hunger. This may progress to more severe neuroglycopenic symptoms including confusion, behavioral changes, personality changes, visual disturbances, seizure, coma and death.^{4,5} The clinical Whipple's triad is used to clinically diagnose one with insulinoma which includes: symptoms known or likely to be caused by hypoglycemia, low plasma glucose measured at the time

of the symptoms and relief of these symptoms when the blood glucose is raised to normal.⁶

In many cases, insulinomas can be localized by non invasive imaging modalities such as CT or MRI. If unrevealing more invasive modalities need to be utilized, such as EUS and insulin sampling via selective arterial calcium stimulation (SACS) and somatostatin receptor scintigraphy. While there is no head to head comparison of EUS and SACS, the sensitivity with SACS may exceed 90% and it is a provocative test with operator dependence and high cost.⁷ C peptide levels, sulfonylurea testing and meglitinides screening are used to rule out factitious causes. If tissue is available, immunohistochemistry (IHC) for insulin chromogranin and synaptophysin aid in confirming the diagnosis. No matter what diagnostic modality one uses, the treatment includes surgical resection vs. enucleation. The pharmacological treatments are available for patients who are poor surgical candidate but only surgery is curative.⁸ The medical management includes frequent carbohydrate meals, octreotide and diazoxide or somatostatin analogs help control hypoglycemic symptoms in only 50-60% of patients.^{9,10}

The most common cause of hypoglycemia in adults is iatrogenic; factitious use of anti-diabetic agents such

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as sulfonoureas or insulin. In healthy adults other causes include lack of hormones such as cortisol or glucagon or hyperinsulinism secondary to nesidioblastosis or autoimmune insulin hypoglycemia.¹¹⁻¹⁴ One of the rare causes of hypoglycemia includes tumors secreting endogenous analogs causing such symptoms. NETs are rare functional tumors of pancreas, they represent a small percentage of all pancreatic tumors (1.3%) but their incidence is rising.¹⁵ Insulinomas causes hypoglycemic episodes secondary to excess endogenous insulin production leading to metabolic derangements. They may exert these effects even when <1 cm in size.

We present 2 cases that exemplify the importance of EUS in accurate diagnosis and location of insulinomas after primary imaging modality was unable to localize the lesion.

CASE # 1

A 65 year old male veteran with past medical history significant for prostate cancer s/p radical prostatectomy presented with episodes of dizziness and weakness. Initially the patient was found to have blood glucose (BG) levels of 40-60s mg/dL and he was unable to raise his glucose levels despite frequent snacks (every 2-3 hours). On presentation, he underwent CT of the abdomen and pelvis which was unremarkable. With consistently low BG levels, his labs revealed an insulin level > 40 mcU/mL (normal 2–25 mcU/mL), c- peptide level of 8 ng/mL (normal 0.78–1.89 ng/mL) and an octreotide scan was negative. With a high suspicion for insulinoma (given the negative sulfonylurea screen) our patient underwent EUS- with fine needle aspiration (FNA). A 14 mm x 16 mm homogenous lesion was noted in the head of the pancreas (Figure 1). The biopsy revealed plasmacytoid neoplastic cells (Figure 2) with pathology positive for chromogranin, synaptophysin and pankeratin and negative for CK 7, CK 19, CK 20 and CDX2. With IHC and staining, a diagnosis of pancreatic endocrine neoplasm was made, and with aspirate positive for insulin, the diagnosis of insulinoma was confirmed (Figure 3). Subsequently the patient underwent enucleation and is currently symptom-free.

CASE # 2

A 67 year-old female with past medical history significant for hypothyroidism, hypertension, recurrent hypoglycemia and hypoglycemia associated seizures was referred for EUS/FNA. She had been having recurrent episodes of hypoglycemia and witnessed

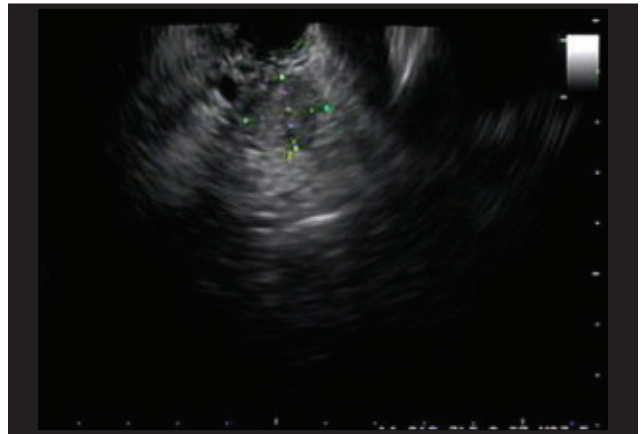


Figure 1. EUS demonstrating lesion case # 1.

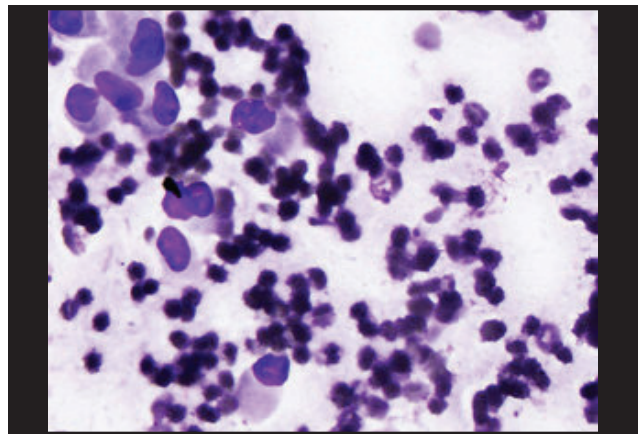


Figure 2. IHC identifying groups of “plasmacytoid” neoplastic cells.

seizures for two years. An abdominal MRI at an outside facility was normal. Her laboratory evaluation revealed an insulin level of 203 mcU/mL (normal 2–25 mcU/mL), c-peptide 44 ng/mL (normal 0.78–1.89 ng/mL) and proinsulin 149.9 pmol/L (normal <18 pmol/L). Screening was negative for sulfonylureas and meglitinides. She underwent EUS/FNA which showed a well-circumscribed hypo- to isoechoic 8.4 mm x 9.6 mm lesion in the head of the pancreas (Figure 4). FNA showed cytology consistent with tumor cells positive for synaptophysin and chromogranin, findings again suggestive of pancreatic neuroendocrine tumor. Similarly this patient underwent surgical resection and IHC was positive for insulin stains and patient is symptom-free.

DISCUSSION

These cases highlight the importance of endoscopic ultrasound in the diagnosis of the insulinoma. The

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diagnosis can be made via biochemical assays and routine blood work although localizing the tumor may prove to be a challenge. The conventional imaging modality such as high resolution pancreatic protocol CT and MRI are often beneficial to localize the lesion. At this time, these modalities are more widely available than EUS. A small number of insulinomas still remain occult after conventional CT scan and MRI fail to identify them.⁹ The sensitivity of CT and MRI has been reported to be 33%-64% and 40%-90%, respectively with MRI being more sensitive and specific when compared to CT.¹⁶⁻¹⁸ A study by Bonato et al. showed that CT was able to localize insulinoma in 4/16 patients with size > 1.5 cm and largest being 12 cm.¹⁹ Both of our cases had hypoglycemia on presentation with abnormal biochemical assay and negative sulfonylurea and meglitinides screen. After initial imaging CT scan and MRI were unable to identify or localize the lesion and strong clinical evidence supportive of insulinoma, EUS localized the lesion and obtained tissue that was helpful to the diagnosis. Preoperative use of EUS for insulinoma allows precise targeting of the lesion, preventing intra-operative (including unnecessary total pancreatectomy) complications, length of operating time and post-surgical complications. With this modern approach, EUS/FNA may also enable carbon-particle tattooing for easy localization. Overall sensitivities up to 94 % are reported in the localization of tumors using EUS.¹⁷ When combined with high resolution CT and EUS the sensitivity increases to 100 %.²⁰ Even with expert surgical experience, there is still a 10-20 % rate of not being able to detect lesion intra-operatively making pre-operative localization very important. The idea is that with precise location the surgical management resection vs. enucleation is more feasible. Key drawbacks for EUS is that it is highly operator dependent, available only in tertiary care centers and has limited utility in localizing lesions in the tail or the distal body of the pancreas or if the tumors are pedunculated or if tumors are extra-pancreatic. Although with advent of intraductal ultrasound, these areas can be readily visualized with its detection rate as high as 90 % of lesion measuring 1-3 mm although it is not widely available.^{21,22} Both of our cases involved lesions in the head of the pancreas. The importance in these cases is that use of EUS aided in the diagnosis and precise localization of even very small (<1 cm) tumors.

Histopathologically, insulinomas stain positive for insulin, pro-insulin, chromogranin A, synaptophysin,

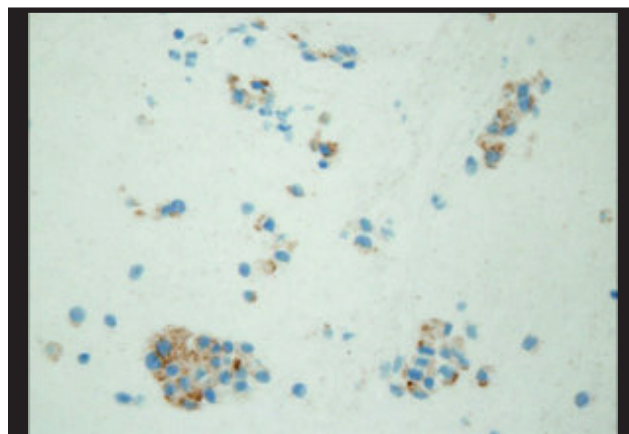


Figure 3. IHC stain for insulin. cells.



Figure 4. EUS demonstrating lesion case # 2

neuron specific enolase and cytokeratin.²³ Our patients' IHC were positive for chromogranin, synaptophysin and pankeratin. Although these markers can be used to identify insulinoma, the importance lies in localizing where the biopsy needs to be taken which can be aided with EUS.

Other techniques such as somatostatin receptor scintigraphy, selective arterial calcium stimulation and hepatic venous sampling are also used to diagnose previously missed tumors. Selective arterial calcium stimulation with hepatic venous sampling for insulin quantification has shown a high sensitivity (93%) for localization, these techniques can get cumbersome and yield can be significantly low.⁷ Combination with EUS allows one major advantage of tattooing and biopsy once tumor is localized.

These cases identify the crucial role of EUS in identifying the lesions which not only confirmed the diagnosis but also aided in the operative resection of the

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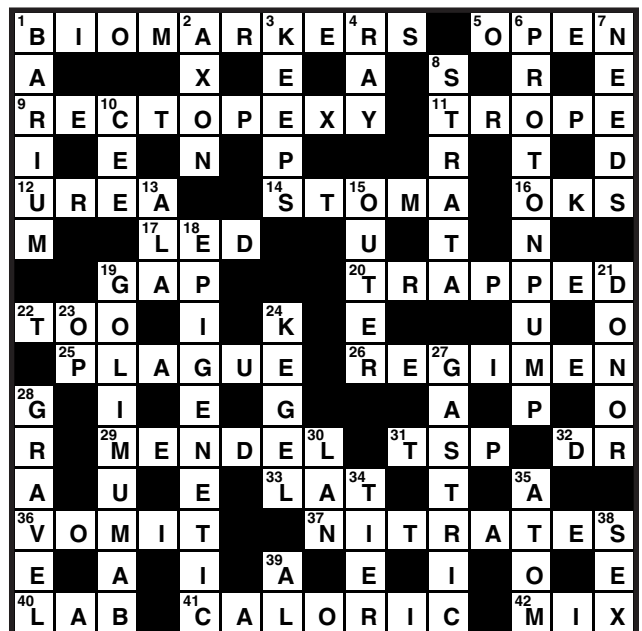
tumors. With the help of EUS, blind surgical approaches are rarely performed. The most common complication post surgery was noted to be hyperglycemia as expected, pancreatic pseudocyst formation, pancreatic fistula, wound infection and the longest hospital stay was 40 days.¹⁹ Once the tumor is identified the curative approach is still enucleation and or distal or partial pancreatectomy. Since the incidence of NET rising it will be critical in identifying the lesions that are missed or are too small to be seen on imaging. Our cases exemplify the important aspects in using primary EUS in diagnosing of insulinoma and management. In addition, cases such as ours can help spread awareness about the utility of EUS in diagnoses that are not amenable per primary imaging modality with strong clinical suspicion for NETs and target the lesion with tattooing for enucleation. Future studies need to be performed that will quantitate variables such as length of hospital stay, pre, intra, and post-operative complications when EUS is used in diagnosis vs. blind approach. ■

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