10.5005/jp-journals-10002-1061
ORIGINAL ARTICLE

Intraoperative Sonographic Localization of Insulinoma: Case Reports and Review of Literature

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ABSTRACT

Insulinomas, a rare clinical entity, are usually small, single, benign and intrapancreatic in location. Several modalities are available for preoperative localization of insulinomas. Intraoperative ultrasound is an important tool used for localization as well as to find anatomical relation of tumor to surrounding tissue. We are reporting three cases of insulinomas with brief discussion on modalities used for localization. After biochemical confirmation of hyperinsulinemia, preoperative localization was done initially by computed tomography followed by intraoperative ultrasonography. Preoperative localization by computed tomography was successful in all the cases but missed an additional lesion in one of the patients which was picked up by intraoperative ultrasonography (IOUS) that changed surgical management. Preoperative localization may not be successful in all the cases. Intraoperative direct inspection, palpation and ultrasound can be used to identify lesions in the cases where preoperative localization was unsuccessful.

Keywords: Hypoglycemia, Insulinoma, Localization, Intraoperative ultrasonography.

INTRODUCTION

Insulinomas are rare and small neuroendocrine tumors. It is the most common (25%) of pancreatic islet cell.[1] Most insulinomas are benign (90% of cases).[2] Virtually all insulinomas are intrapancreatic, rarely (2%) extrapancreatic and may present with symptoms of hypoglycemia.[2] In its sporadic form (90%) tumors are generally solitary, whereas in its familial form (5-10%) they are multiple, especially in the setting of the multiple endocrine neoplasia (MEN) type 1 syndrome. Approximately 80 to 90% of insulinomas are less than 2 cm in size and the lesions are distributed equally throughout the head, body and tail of the pancreas. Although insulinoma may occur throughout life, the mean age at presentation is 45 years (range 8-82) with a female preponderance (female to male ratio 1.4:1). We are presenting three cases of insulinoma diagnosed during March 2009 to April 2010 employing intraoperative ultrasonography.

PATIENTS AND METHODS

Case 1

A 24-year-old male presented to emergency department with symptoms of neuroglycopenia. His blood glucose was 45 mg/dl and symptoms improved after oral glucose ingestion. He had history of recurrent dizziness, sweating and palpitations in fasting state for 4 months that was relieved by eating. There was no history of unconsciousness, seizures, headache or chest pain. General and systemic examination was unremarkable. His body mass index (BMI) was 26 kg/m^2 and he looked apparently healthy. Family history was insignificant. He was investigated for insulinoma in endocrine unit.

Case 2

A 38-year-old female gave history of recurrent neuroglycopenic symptoms in fasting state for last 4 years that included episodic diaphoresis, shaking of hands and feeling of weakness. These symptoms were relieved after eating. Once she became unconscious and found to be hypoglycemic, she was treated by 25% dextrose infusion. Her BMI was 28.2 kg/m^2 and menstrual cycles were normal. She did not have any chronic medical illness in the past and denied history of any drug intake. Routine investigations turned out to be normal. He was investigated in endocrine unit for insulinoma.

Case 3

A 50-year-old obese female with BMI of 34.4 kg/m^2 presented with recurrent episodes of hypoglycemia during early morning hours for last 3 years. She has gained 6 kg weight in past 2 years and had one episode of generalized seizures associated with unconsciousness that responded to dextrose infusion. She was referred to endocrine unit for evaluation of insulinoma.

RESULTS

Case 1

Patient developed hypoglycemia after 6 hours of fasting under supervision. His biochemical profile at the end of fast revealed, blood glucose: 30 mg/dl, serum insulin: 19 µIU/ml, C-peptide: 1062 pmol/L. This suggested diagnosis of endogenous hyperinsulinemia. Imaging was done to localize islet cell tumor. Triple phase contrast-enhanced computed tomography (CECT) of abdomen by GE 64 slice light speed VCT (GE Healthcare USA) demonstrated a suspicious lesion 2 × 2 cm in body of pancreas showing minimal enhancement on contrast. The patient was referred to surgical oncology unit for further management. During surgery after inspection and manual palpation intraoperative ultrasonography (IOUS) was done using Sonosite Micromaxx USG (Sony Japan), which detected another lesion of size 1.5 × 1 cm in addition to previous lesion (Fig. 1). Both lesions were homogeneously hypoechoic in comparison to rest of pancreatic tissue. In view of these two lesions, distal pancreatectomy with splenectomy was performed which revealed two nodules, both well-circumscribed measuring 2 × 1.5 × 1.3 cm and 1.3 × 1 × 1 cm respectively. Both pre and postoperative serum calcium and phosphorus were in normal range. During postoperative period his blood sugar started rising which was treated by insulin. The histopathology was consistent with diagnosis of insulinoma in both lesions and there were no features of metastasis or lymph node involvement.

Case 2

Patient became symptomatic for hypoglycemia after 4.5 hours of fast and at that time her blood glucose was 33 mg/dl, serum insulin was 11.5 µIU/ml, and serum C-peptide was 1238 pmol/L. Triple phase CECT of abdomen revealed an intensely blushing small mass in uncinate process of pancreas. Diagnosis of pancreatic solitary insulinoma was made and patient was referred to surgical oncology department for surgery. During surgery, intraoperative USG confirmed presence of the above mentioned lesion in uncinate process which was enucleated. The mass was 1.5 × 1.4 cm in size and histopathological examination was consistent with diagnosis of insulinoma (Fig. 2). Patient's blood glucose improved to normal after surgery.

Case 3

This patient became hypoglycemic after 9 hours of fast. Her biochemical profile at that time showed blood glucose: 45.9 mg/dl, serum insulin: 11.4 µIU/ml and C peptide: 808 pmol/L. Triple phase CECT of abdomen revealed a suspicious lesion in tail of pancreas. Intraoperative ultrasonography (IOUS) detected another lesion within body of pancreas. Since lesion in tail was very close to splenic hilum, distal pancreatectomy with splenectomy was done taking out both the lesions. Patient improved after surgery but became hyperglycemic which was managed with insulin. Interestingly, histopathological examination revealed presence of insulinoma in one of the lesions that was suspected by IOUS only.

REVIEW OF LITERATURE

Insulinomas, although rare, are most common cause of hyperinsulinemic hypoglycemia in the adult population. The association between hyperinsulinism and a functional islet cell tumor was first established by Wilder et al[3] when they performed an operation in a patient with hypoglycemia and found an islet cell carcinoma with hepatic metastases. Insulinomas invariably present with signs and symptoms related to hypoglycemia, and as described by "Whipple's triad", hypoglycemia and neuroglycopenic symptoms that are corrected by the administration of carbohydrate are the hallmarks of the diagnosis of insulinoma.[4] For many years, well before tests for determination of insulin and proinsulin were readily available, the 72-hour monitored fast was the cornerstone for diagnosis. However, in more than 97% of individuals, a supervised fast of 48 hours with biochemical testing, including plasma insulin and proinsulin measurements every 6 hours, is sufficient to diagnose

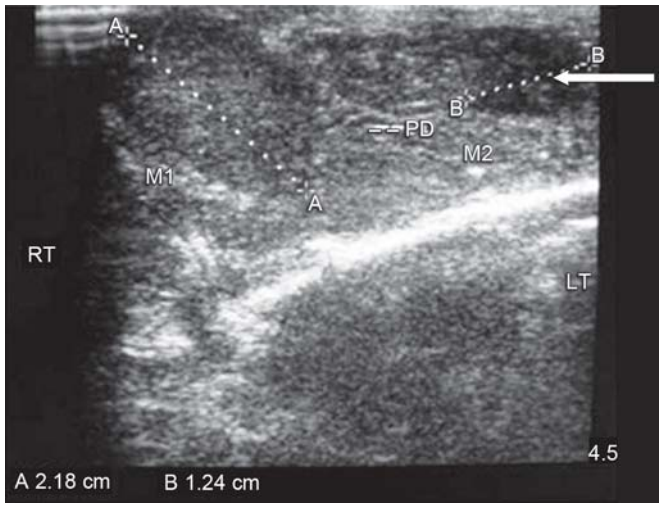

Fig. 1: IOUS showing both lesions, the second lesion (arrow) was nonlocalized on CECT

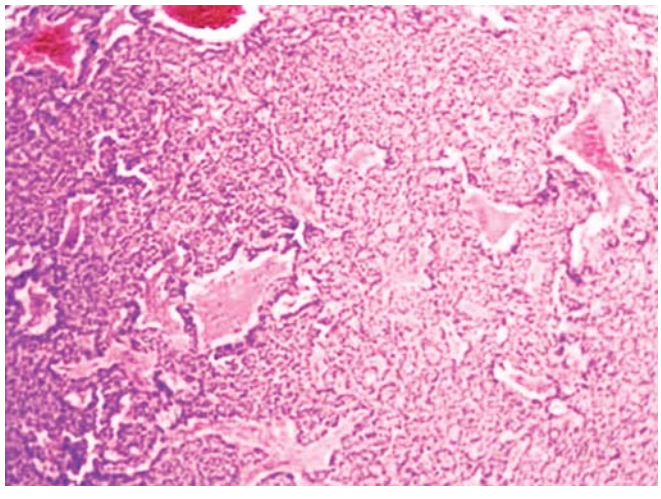

Fig. 2: Microscopic features of the insulinoma. Tumor cells arranged in ribbon-like trabeculae and acinar pattern in the background of pink homogeneous amyloid (H & E stain × 200)

insulinoma.[5,6] The endocrine society proposed criteria which state that the findings of hypoglycemic symptoms, signs, or both with plasma concentrations of glucose less than 55 mg/dl (3.0 mmol/liter), insulin of at least 3.0 μU/ml (18 pmol/liter), C-peptide of at least 0.6 ng/ml (200 pmol/liter), and proinsulin of at least 5.0 pmol/liter documents endogenous hyperinsulinism.[7] After establishing a diagnosis of insulinoma, a variety of imaging modalities with different sensitivities can localize the tumor. The role of preoperative imaging is crucial for two reasons. First, imaging is used to evaluate evidence of metastatic disease; second, localization can better facilitate discussions with the patient as regard to extent and type of operation. Because virtually all sporadic insulinomas are small and intrapancreatic, preoperative localization fails 10 to 27% of the time. Various modalities can be used for localization including transabdominal ultrasound, multiphase helical computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SRS). The success rate of transabdominal ultrasound for localization varies widely across institutions from 9 to 66%.[8] Multiphase helical CT localizes 50 to 80%, MRI 40 to 70%, and SRS 17% of all insulinomas.[8] All of the these imaging studies combined can localize around 80% of tumors.[8,9] CT and MRI are useful to evaluate for metastatic disease, although MRI may be more sensitive than CT in identifying liver metastases.[10]

When preoperative noninvasive studies fail to localize tumors, invasive studies may aid in regional localization. Pancreatic arteriography and transhepatic portal venous sampling (THPVS) was historically used for localization but in spite of cumbersome methodology, sensitivity for localization varied 25 to 40% and 77 to 100% respectively.[5,10] THPVS has been replaced by intra-arterial calcium stimulation (IAC), which relies on calcium as a secretagogue for insulin secretion from the tumor. IAC has a reported sensitivity from 80 to 94% in localizing insulinomas to a particular region of the pancreas.[9,11] The use of endoscopic ultrasound for tumor localization has steadily increased over the past several years with reported sensitivities ranging from 40 to 93%.[12] The use of intraoperative ultrasound (IOUS) introduced in 1981, is useful to localize intrapancreatic nonpalpable lesions and to determine the proximity of those lesions to the pancreatic or biliary duct. IOUS performed during an open or laparoscopic exploration can localize an insulinoma.[11,13] Laparoscopic exploration and ultrasonography have been utilized for localization of sporadic insulinomas with reported success rate of 86%.[14] In addition, IOUS can precisely demonstrate the relationship of tumor to the pancreatic and common bile duct, portal vein, splenic and superior mesenteric blood vessels.

Although preoperative localization using CECT was successful in all of our cases, but it failed to detect a second lesion in first patient. This lesion was later picked up by intraoperative ultrasound, which changed the course of surgery. Retrospective analysis of CT scan was done but it failed to visualize the missing lesion. Moreover, the use of this modality is of special importance in centers like ours, where availability of state-of-art newer techniques like intra-arterial calcium stimulation (IAC) are not available as well as the patients do not afford such expensive technique.

We reviewed literature published on preoperative localization of insulinomas. There have been numerous publications questioning the real need for aggressive preoperative localization. A retrospective review by K Ravi and Britton (2007) showed that localization rate for preoperative noninvasive and invasive test is 25% and 48% respectively. Intraoperative inspection and palpation localized the lesions correctly in 91% and intraoperative ultrasound in 93% of cases, out of five occult tumors (indeterminate anatomical site before operation) all were palpable at surgery and four of these were also correctly identified by intraoperative ultrasound.[14] In another case series by C Juanco Pedregal et al (1996), out of six unlocalized insulinomas five were picked up by intraoperative ultrasound (IOUS) and remaining lesion was also picked up 3 years later by IOUS.[15] In some case series, the localization rate for combined manual palpation and IOUS was 100%.[16,17]

CONCLUSION

While preoperative noninvasive localization studies are able to detect the insulinomas in majority of patients, intraoperative direct inspection and palpation with ultrasound can be used to identify lesions in cases where preoperative localization is unsuccessful. Intraoperative ultrasound is particularly helpful in delineating the spatial relationship of the tumor with the pancreatic duct and major vessels and helps the surgeon to choose between resection and enucleation. A combination of intraoperative direct inspection, manual palpation and ultrasound will be superior most for localization of insulinomas.

REFERENCES

1. Pasieka JL, McLeod MK, Thompson NW, et al. Surgical approach to insulinomas: Assessing the need for preoperative localization. Arch Surg 1992;127:442-47.
2. Jani N, Moser AJ, Khalid A. Pancreatic endocrine tumors. Gastroenterol Clin North Am 2007;36:431-39.
3. Wilder RM, Allan FN, Power MH, et al. Carcinoma of the islets of the pancreas: Hyperinsulinism and hypoglycemia. J Am Med Assoc 1927;89:348-55.
4. Whipple AO, Frautz VK. Adenomas of islet cells with hyperinsulinism: A review. Ann Surg 1935;101:1299-1335.
5. Yao JC, Rindi G, Evans DB. Pancreatic endocrine tumors. In: Devita Jr VT, Hellman S, Rosenberg SA (Eds). Cancer principles and practice of oncology (8th ed). Philadelphia: Lippincott Williams and Wilkins 2007;1702-16.
6. Hirshberg B, Andrea L, Bartlett DL, et al. Forty-eight-hour fast: The diagnostic test for insulinoma. J Clin Endocrinol Metab 2000;85:3222-26.
7. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009;94(3):709.
8. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol 2005;19:783-98.
9. Guettier JM, Kam A, Chang R, et al. Localization of insulinomas to regions of the pancreas by intra-arterial calcium stimulation: The NIH experience. J Clin Endocrinol Metab 2009;94:1074-80.

10. Nikfarjam M, Warshaw AL, Axelrod L, et al. Improved contemporary surgical management of insulinomas: A 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247:165-72.
11. Brown CK, Bartlett DL, Doppman JL, et al. Intra-arterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. Surgery 1997;122: 1189-94.
12. Anderson MA, Carpenter S, Thompson NW. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol 2000;95:2271-77.
13. Grover AC, Skarulis M, Alexander R, et al. A prospective evaluation of laparoscopic exploration with intraoperative ultrasound as a technique for localizing sporadic insulinomas. Surgery 2005;138:1003-08.
14. Ravi K, Britton BJ. Surgical approach to insulinomas: Are preoperative localization tests necessary? Ann R Coll Surg Engl 2007;89:212-17.
15. Pedregal CJ, et al. Insulinomas, usefulness of intraoperative ultrasound. European Journal of Ultrasound 1996;4:185-89.
16. Galiber AK, Reading CC, Charboneau JW, Sheedy PF, James EM, Gorman B, Grant CS, van Heerden JA, Telander RL. Localization of pancreatic insulinoma: Comparison of pre and intraoperative US with CT and angiography. Radiology 1988;166:405-08
17. Gorman B, Charboneau JW, James EM, Reading CC, Galiber AK, Grant CS, van Heerden JA, Telander RL, Service FJ. Benign pancreatic insulinoma: Preoperative and intra-operative sonographic localization. Am J Radiol 1986;147: 929-34.