

Endoscopic Localization and Tattooing of a Proinsulinoma for Minimally Invasive Resection

Annabelle Rodriguez, MD, Marcia I. Canto, MD, MHS, and Martin A. Makary, MD, MPH

Abstract: Hypoglycemia can be common in patients using insulin injections or certain antidiabetes medications. In rare cases, hypoglycemia can be caused by a pancreatic insulinoma. We report a case of a 33-year-old woman found to have severe recurrent hypoglycemia. Diagnostic studies such as continuous glucose monitoring and a hospitalized fast provided biochemical evidence for a proinsulinoma. After abdominal multidetector contrast-enhanced computerized tomography failed to detect pancreatic abnormalities, endoscopic ultrasonography identified and localized a 9-mm pancreatic tail lesion. At the time of endoscopy, the lesion was tattooed with ultrasonographic guidance for subsequent laparoscopic visualization and curative resection.

Key Words: insulinoma, proinsulinoma, hypoglycemia, laparoscopy, endoscopic ultrasound

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CASE REPORT

A 33-year-old woman presented to a tertiary academic medical center for evaluation of hypoglycemia. Before her visit to our institution, she had been previously evaluated for anxiety symptoms and was prescribed sertraline 200 mg/d orally. She underwent laboratory testing that identified fasting plasma glucose of 47 mg/dL. A subsequent endocrinology consultation revealed normal thyroid function tests, normal cortisol levels after adrenocorticotropic hormone stimulation testing, as well as normal insulin and C-peptide levels. She had been instructed to monitor her blood glucose with a glucose meter and eat frequent meals. At our institution, she reported frequent episodes of hypoglycemia, with blood glucose frequently between 30 and 40 mg/dL. Episodes resolved with ingestion of food or sweetened beverages. Her husband reported that, oftentimes, she was difficult to arouse in the early morning, but she had never experienced a seizure-like episode. She reported having gained more than 30 lb in less than 1 year. Her medical history was unremarkable except for the diagnosis of anxiety. Family history was negative for tumors compatible with multiple endocrine neoplasia. Physical examination revealed a well-developed, well-nourished, white woman in no distress, with a normal physical examination.

To verify the presence, frequency, and severity of hypoglycemic episodes, the patient was instructed to wear a blinded continuous glucose sensor monitoring system (Medtronic CGMS) for 72 hours. She was prescribed glucagon 1 mg intramuscularly to be used by her husband in the event he was unable to arouse her from sleep. As shown in Figure 1A, CGMS tracings showed

the normal range of glucose to be defined between a low of 70 mg/dL (blue line) and an upper limit of normal of 180 mg/dL (orange line). Within hours of the CGMS placement, she demonstrated glucose readings less than 60 mg/dL, with the longest duration occurring during the overnight period. On Sunday morning, her husband administered the glucagon 1 mg intramuscularly because she was not arousable from sleep. The glucagon promptly elevated her glucose levels, and she became alert and responsive to her husband.

The findings from the CGMS tracings prompted a supervised hospitalized fast to obtain biochemical studies for a possible insulinoma. During the supervised fast, the patient experienced symptomatic hypoglycemia within 6 hours and promptly returned to the normal range after administration of glucagon 1 mg intravenously (Fig. 1B). Baseline insulin and C-peptide levels were normal (6 μ IU/mL and 2 ng/mL, respectively), with a corresponding plasma glucose of 70 mg/dL, whereas proinsulin levels were elevated at 38.9 pmol/L. Plasma sulfonylurea screen was negative, and insulinlike growth factor II levels were normal (734 ng/mL). At the 6 hours' time point, proinsulin levels remained elevated (37.9 pmol/L) when plasma glucose decreased to 38 mg/dL, whereas insulin (5.3 μ IU/mL) and C-peptide (1.7 ng/mL) levels remained inappropriately in the normal range. The search for an insulinoma began; however, no pancreatic abnormalities were visualized on a state-of-the-art 64-slice multidetector row computed tomography (CT), with a pancreas protocol to capture arterial and venous phases at 30 and 60 seconds postinjection, respectively. Our 3-dimensional CT uses cross-sectional images 0.75 mm in thickness with 0.5 mm interscan spacing. Subsequent review did not demonstrate any pancreatic abnormalities. To investigate further, we performed a transgastric endoscopic ultrasound (EUS) of the pancreas.

Outpatient EUS performed with sedation discovered an isolated 9-mm soft tissue hypoechoic mass lesion with discrete borders in the pancreatic tail with normal pancreas elsewhere (Fig. 2). Endoscopic ultrasound-guided fine-needle aspiration was performed during the same session. Because the lesion was small and its location in the center of the gland would make it very difficult to find with laparoscopy, the lesion was tattooed during the EUS procedure by injecting sterile purified carbon particles (GI Spot; GI Supply, Camp Hill, Pa). Under ultrasound visualization, this dye was injected immediately adjacent and proximal to the lesion for easy visualization at the time of laparoscopy. The patient subsequently underwent a laparoscopic distal pancreatectomy with spleen preservation without complications. The tattoo was readily identified and demarcated a precise line of resection (Fig. 3).

The night before the operation, the patient was hospitalized for blood glucose management while fasting overnight before the surgical procedure. Even with a continuous intravenous glucose infusion of 10% dextrose and multiple injections of 50% glucose ampoules, the patient's blood glucose level precipitously dropped 3 times from 100 to 140 mg/dL to 40 to 50 mg/dL while fasting for surgery. Conversely, immediately upon removing the pancreatic lesion during the operation, the

From the Johns Hopkins University, School of Medicine, Baltimore, MD. Received for publication August 18, 2010; accepted November 8, 2010. Reprints: Annabelle Rodriguez, MD, Johns Hopkins Bayview Medical Center, Division of Endocrinology and Metabolism, Mason F. Lord Bldg, Center Tower, Room 639, 5200 Eastern Ave, Baltimore, MD 21224 (e-mail: arodrig5@jhmi.edu). Copyright © 2011 by Lippincott Williams & Wilkins

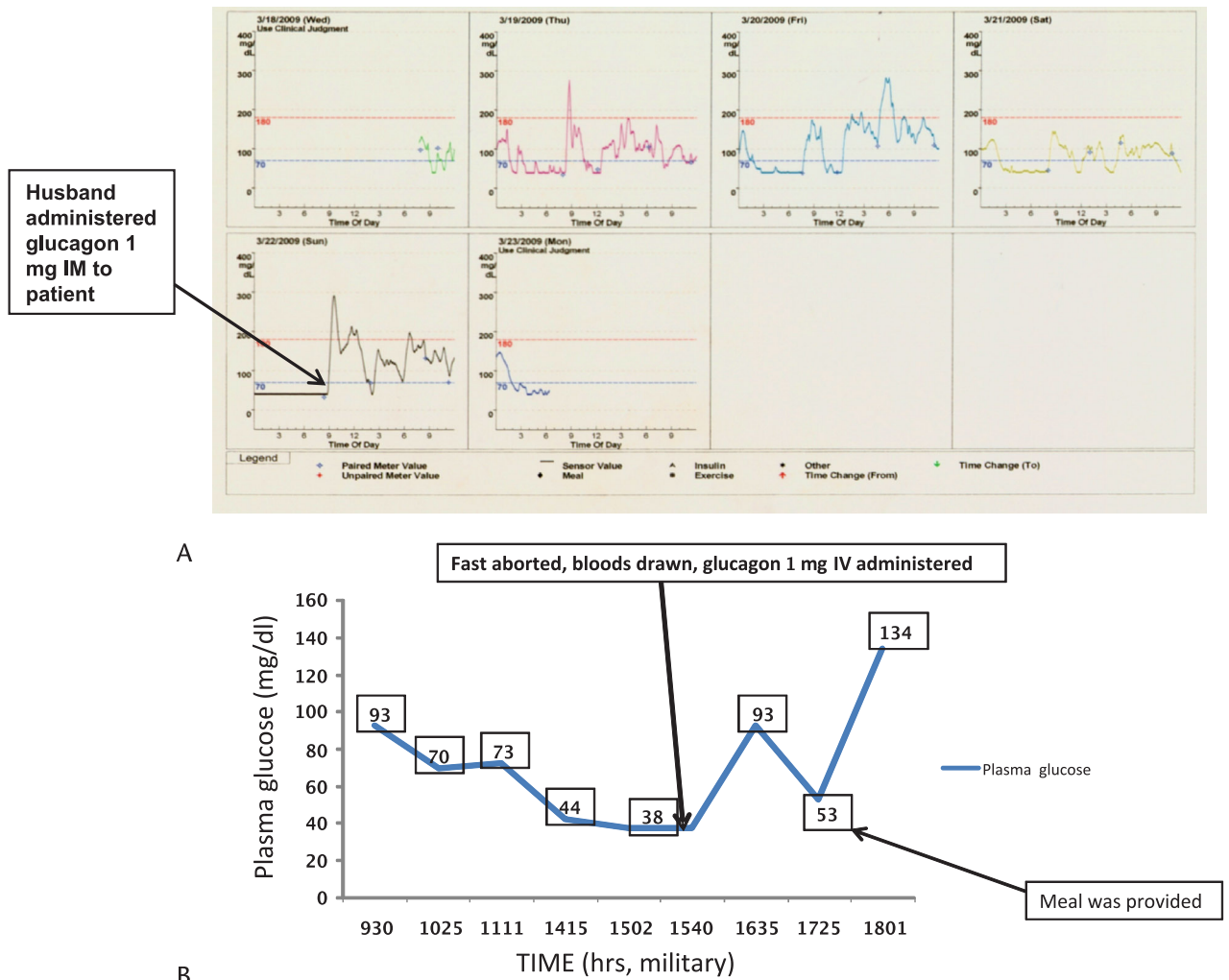


FIGURE 1. Biochemical studies confirming severe recurrent hypoglycemia. A, Patient was instructed to wear a Medtronic continuous glucose monitoring system for 72 hours. Glucose levels below the dashed blue horizontal line are less than 70 mg/dL, whereas levels above the dashed orange horizontal line are higher than 180 mg/dL. The arrow highlights the glucose response after the patient’s husband administered glucagon 1 mg intramuscularly to the patient because she was not arousable. B, Plasma glucose levels during a supervised fast. Within 6 hours of the fast, the patient experienced symptomatic hypoglycemia, at which time the fast was aborted, and appropriate laboratory studies were drawn.

patient’s blood glucose levels normalized without any subsequent episodes of hypoglycemia. The patient was discharged from the hospital on postoperative day 4 on a regular diet without any medications needed for glucose control or pain. Overnight fasting laboratory studies on the day of discharge revealed normal levels of glucose (91 mg/dL), insulin (4.9 μ IU/mL), C-peptide (1.0 ng/mL), and proinsulin (8.5 pmol/L). Follow-up 2 months later revealed no recurrent hypoglycemic episodes or new-onset hyperglycemia.

DISCUSSION

The incidence of pancreatic adenomas secreting proinsulin or insulin is rare.¹ The most characteristic presenting complaint are symptoms related to hypoglycemia (ie, hyperadrenergic symptoms such as anxiety, nervousness, and hunger). As a consequence of ingestion of frequent meals, substantial weight gain is also a common complaint. As an intermediate diagnostic step before the standard hospitalized supervised fast, we had the patient wear the CGMS device for 72 hours. This device

has been shown to be of value in the management of hypoglycemia in persons with diabetes,² but to our knowledge, only 2 studies have previously reported the use of CGMS for the evaluation of the frequency and severity of hypoglycemic episodes in adults not known to have diabetes.^{3,4} Our results were consistent with these studies in demonstrating the presence, frequency, and severity of nocturnal hypoglycemia in our patient. Of additional clinical benefit was the documentation of rapid normalization to euglycemia after the patient’s husband had administered glucagon intramuscularly (Fig. 1A).

Endoscopic ultrasonography is an established technique for visualization and localization of pancreatic lesions, including endocrine tumors. In particular, when a CT is unremarkable, it can confirm the diagnosis of a biologically active endocrine tumor, in this case a proinsulinoma, when the patient demonstrates symptoms. Endoscopic ultrasound can also localize single or multiple tumors to guide the operative plan. The sensitivity and specificity of EUS for detection of pancreatic endocrine tumors, including insulinomas, are 83%⁵ to 93%⁶ and 83.7%⁷ to

95%,⁵ respectively. Because of its high sensitivity and specificity, preoperative EUS can direct patient management and increase the cost-effectiveness of localization of pancreatic endocrine tumors (caused by a decreased use of traditional procedures for localization such as diagnostic angiograms and venous sampling procedures).⁸ Endoscopic ultrasound-guided tattooing is a new endoscopic technique^{9,10} that provides a safe and convenient means of marking a tumor so that it can be readily localized at the time of surgery.

Intraoperative localization of small pancreatic endocrine tumors is a notorious surgical challenge. Wide and blind resections of the tail of the pancreas when preoperative localization methods fail were, and remain, common. Sometimes requiring hours to find during the operation, the imprecision in localizing these tumors can also result in an inappropriate surgical margin of resection, increased operative time, and iatrogenic diabetes. In some instances, failure to remove the tumor, even after a blind resection, has been described. The challenge of where to resect the pancreas can present a difficult clinical dilemma. Dividing the pancreas too far away from the tumor unnecessarily sacrifices healthy pancreatic islets and can result in iatrogenic diabetes. Conversely, dividing the gland too close to the tumor can result in inappropriate oncologic margins. In the reported case, we addressed this dilemma using a tattoo placed with EUS guidance for precise localization.

Laparoscopy for pancreatic tumors has many benefits for the patient compared with the traditional open operation; however, the challenge of finding a small pancreatic tumor has historically mandated an open surgical approach to allow the surgeon to manually palpate the gland oftentimes using a high-definition intraoperative ultrasound. Because of the decreased haptic feedback of laparoscopy, making palpation difficult, removing a small pancreatic tumor laparoscopically has been considered to be a blind and hazardous resection. To address this problem, we describe that tattooing enables the surgeon to perform a precise laparoscopic resection. This single method of localization allows the patient to benefit from the minimally invasive approach. Laparoscopy is associated with decreased postoperative pain, shorter length of hospital stay, improved cosmesis, and fewer complications, such as wound infections.^{11,12} In addition, splenic preservation is more feasible with a laparoscopic approach given the increased magnification used during the procedure.^{13–15}

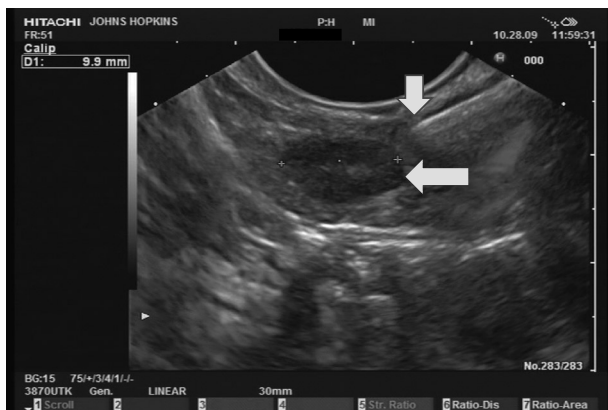


FIGURE 2. Endoscopic ultrasound image of pancreas. A hypoechoic oval 9-mm lesion was localized in the pancreatic tail with discrete borders (left arrow) and needle tip (down arrow) at pancreatic surface before injection with tattoo.

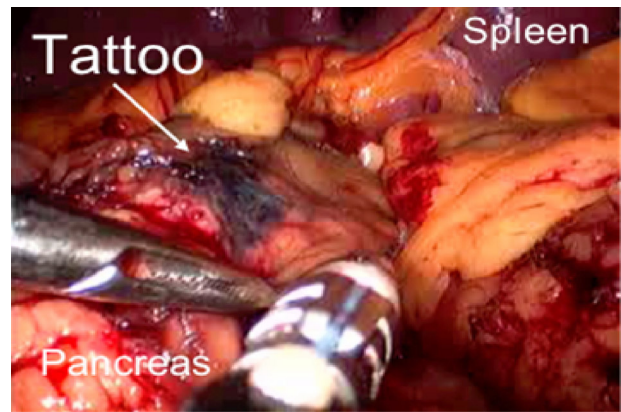


FIGURE 3. Laparoscopic visualization of tattooed pancreatic lesion. Localization with ink preoperatively allows for a precise laparoscopic surgical resection. The inferior border of the pancreatic tail is being divided with a 5-mm thermal sealing instrument (white-tipped device) that also cuts the tissue being sealed.

Our experience with this case report is entirely consistent with recent management guidelines issued by the North American NeuroEndocrine Tumor Society.¹⁶ In addition, the use of the tattoo by EUS and the laparoscopic approach contributed to substantially reduced morbidity in the curative treatment for this patient.

Therefore, we report a novel management plan for patients with a small pancreatic tumor, optimizing preservation of normal pancreatic islets and allowing laparoscopic removal. This approach uses the precision of EUS and confers to the patient the decreased surgical risks associated with minimally invasive surgery.

REFERENCES

- Goldin SB, Aston J, Wahi MM. Sporadically occurring functional pancreatic endocrine tumors: review of recent literature. *Curr Opin Oncol.* 2008;20:25–33.
- Ryan EA, Germsheid J. Use of continuous glucose monitoring system in the management of severe hypoglycemia. *Diabetes Technol Ther.* 2009;11:635–639.
- Munir A, Choudhary P, Harrison B, et al. Continuous glucose monitoring in patients with insulinoma. *Clin Endocrinol.* 2008;68:912–918.
- Wang X. Application of the continuous glucose monitoring system in the 72-hour fast test in two patients with hypoglycemia. *Diabetes Technol Ther.* 2005;6:883–886.
- Ardengh JC, Rosenbaum P, Ganc AJ, et al. Role of EUS in the preoperative localization of insulinomas compared with spiral CT. *Gastrointest Endosc.* 2000;51:552–555.
- Anderson MA, Carpenter S, Thompson NW, et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol.* 2000;95:2271–2277.
- Sotoudehmanesh R, Hedayat A, Shirazian N, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. *Endocrine.* 2007;31:238–241.
- Bansal R, Tierney W, Carpenter S, et al. Cost effectiveness of EUS for preoperative localization of pancreatic endocrine tumors. *Gastrointest Endosc.* 1999;49:19–25.
- Zografos GN, Stathopoulou A, Mitropapas G, et al. Preoperative imaging and localization of small sized insulinoma with EUS-guided fine needle tattooing: a case report. *Hormones (Athens)* 2005;4:111–116.

10. Gress FG, Barawi M, Kim D, et al. Preoperative localization of a neuroendocrine tumor of the pancreas with EUS-guided fine needle tattooing. *Gastrointest Endosc*. 2002;55:594–597.
11. Baker MS, Bentrem DJ, Ujiki MB, et al. A prospective single institution comparison of perioperative outcomes for laparoscopic and open distal pancreatectomy. *Surgery*. 2009;146:635–643.
12. Nakeeb A. Laparoscopic pancreatic resections. *Adv Surg*. 2009;43:91–102.
13. Warshaw AL. Distal pancreatectomy with preservation of the spleen. *J Hepatobiliary Pancreat Sci*. 2010;17:808–812 [Epub ahead of print].
14. Nau P, Melvin WS, Narula VK, et al. Laparoscopic distal pancreatectomy with splenic conservation: an operation without increased morbidity. *Gastroenterol Res Pract*. 2009;2009: 846340–846345.
15. Pryor A, Means JR, Pappas TN. Laparoscopic distal pancreatectomy with splenic preservation. *Surg Endosc*. 2007;21:2326–2330.
16. Vinik AI, Woltering EA, Warner RRP, et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas*. 2010;39:713–734.