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Case Report

Recovery of hypoglycemia symptoms after insulinoma negative pancreatic surgery: Case series

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Abstract
Insulinoma, one of the most common endocrine tumors of the pancreas, is usually benign, solitary and has an intrapancreatic location. Precise localization of insulinoma is important for curative treatment.
This study looks at 5 patients who underwent operation for insulinoma. The median age, body mass index, preoperative insulin and C-peptide levels, and length of hospital stay were 36 years, 27 kg/m2, 32 µU/ml, 7ng/ml and 21 days, respectively. An endoscopic ultrasound (EUS) and intraoperative ultrasound (I-OUS) were conducted on all of the patients. Enucleation was performed on 3 patients and distal pancreatectomy ± splenectomy on 2 patients. Furthermore, the histopathological examination conducted on the patients showed insulinoma in 3 patients and granulomatous lymphadenitis in 1 patient, with one observed to have normal pancreas tissues. Following the operation, the glucose level of all patients was found to be within a normal range.
Distal pancreatectomy and enucleation can only be performed after determining precise localization of insulinoma via EUS and I-OUS.

Keywords: Insulinoma; Enucleation; Distal Pancreatectomy; Endoscopic Ultrasonography (EUS); Intraoperative Ultrasonography (I-OUS).

INTRODUCTION

The most common neuroendocrine tumor of the pancreas is insulinoma, a rare and often benign tumor of the pancreas, which occurs in 1-4 / 1000000 people of the general population (1). The symptoms associated with insulinoma are known as the Whipple triad: symptoms known or likely to be caused by hypoglycemia, especially after fasting or heavy exercise; a low plasma glucose measured at the time of the symptoms; and relief of symptoms when the glucose is raised to normal (2). The symptoms and insulin levels are important for the diagnosis of insulinoma. As of recently, preoperative endoscopic ultrasonography (EUS) and intraoperative ultrasonography (I-OUS) have been increasingly used for the purpose of localizing the insulinoma (3,4). However, despite the advanced preoperative and / or intraoperative imaging methods, localization of insulinoma is still difficult to detect. The main treatment method for insulinoma is surgery, with enucleation being a frequently performed surgical method (5). Distal pancreatectomy is an effective treatment option for multi-focal, malignant insulinoma and for corpus or tail of pancreatic insulinoma (6-8). In the present study, we aimed to report on the management of insulinoma patients, and to conduct an assessment of the performance of EUS and I-OUS in terms of localization of insulinoma.

CASE REPORT

Patients

The study included five patients, who between the dates of February 2015 and November 2016 had undergone surgery for insulinoma. Patients' demographic characteristics, preoperative laboratory and imaging methods, operation methods, and postoperative course were recorded from hospital data, operation notes, and patient files (Tables 1 and 2). Prior to conducting the study, informed consent was received from all patients.

Surgical technique

After receiving a diagnosis of insulinoma, all patients underwent a laparotomy. The operative field was shaved and cleaned with povidone-iodine 10% solution following administration of general anesthesia. A bilateral subcostal incision was made on all patients. Liver, hilus of the spleen, peritoneum and pelvis were evaluated in terms of metastatic peritoneal implants. The greater omentum was carefully dissected between the stomach

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and transverse colon beyond the gastroepiploic arches using a 5-mm abdominal ligasure (Ligasure®, Metronic-Covidien, Minneapolis, USA). The pancreas was identified, along with adjacent tissues and organs. A routine examination was performed on major vascular structures, such as the superior mesenteric vein, splenic vein, and portal vein before performing both a pancreas palpation and I-OUS to localize the insulinoma, with the latter being performed by a radiologist. Enucleation was performed to obtain negative surgical margin. Spleen preserving distal pancreatectomy was performed using an 80-mm linear stapler with primary sutures (3/0 silk) following the dissection of the splenic hilus and splenic artery and vein. In the patients who underwent a splenectomy, the spleen was lifted and dissected from splenophrenic ligament and splenocolic ligament. Splenic artery and vein were ligated with 3-0 Polyglactin Plus. An en-bloc splenectomy and distal pancreatectomy were performed. Monopolar or bipolar electrocautery and primary sutures were used to achieve homeostasis. On the basis of the results of the enucleation or distal pancreatectomy, a drain was placed in the surgical site after irrigation with 0.9 % NaCl. The abdomen was then closed anatomically. The patients were followed-up at the end of the first, third and sixth months, at which times blood glucose level and other biochemical parameters were measured.

RESULTS

The median age of the patients was 36 years (min –max: 34-79) and median body mass index (BMI) was 27 kg/m2 (min –max= 25-32). Three of the patients were male and two female. The history of the patients showed that they experienced cold sweats, weakness, syncope attacks, palpitations and hypoglycemia symptoms, and all had the Whipple triad (2). The median initial symptom time was 4 months (min –max: 2-9). The preoperative lowest blood glucose of the patients was 28 mg/dl. A prolonged fasting test was performed on all patients, from which it was detected that they each had hyperinsulinemia. The median preoperative insulin level was 32 uU/ml (min –max= 8 -41) (Table 1), and the median preoperative C-peptide level was 7ng/ml (min –max= 2-32). Preoperative EUS was performed on all patients and preoperative localization of the insulinoma was determined (Figures 1,2)

Table 1. Patients and characteristics

No	Age	Gender	BMI (kg/m2)	Initial symptom (months)	Whipple triad	Lowest glucose (mg/dl)	Preop Insulin (uU/L)	Preop -Peptide (ng/ml)	EUS	I-USG
1	34	E	25	2	Yes	38	32	7	Head	Head
2	27	K	27	4	Yes	28	8	2	Corpus	Corpus
3	36	K	25	3	Yes	45	32	32	Corpus-Tail	Doubted
4	49	E	32	8	Yes	47	27	6	Tail	Tail
5	79	E	28	9	Yes	29	41	8	Corpus	Doubted

BMI= Body Mass Index, Preop= Preoperative, EUS= Endoscopic ultrasonography, I-OUS= Intraoperative ultrasonography

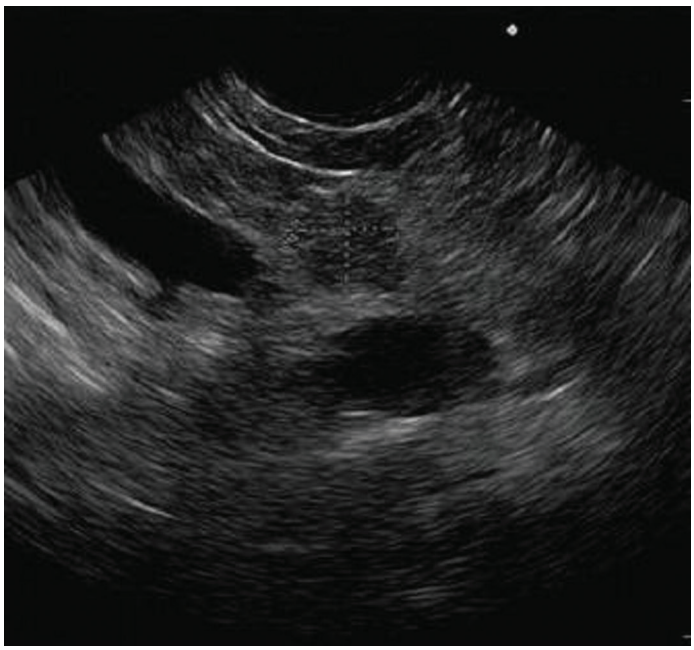

Figure 1. Preoperative EUS imaging

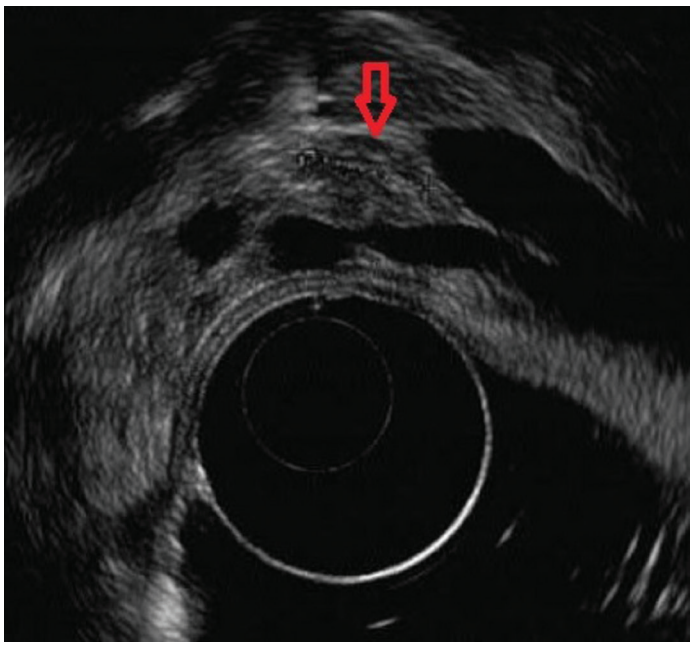

Figure 2. Appearance of insulinoma with EUS

During the operation, blood glucose level was measured regularly. Localization of insulinoma was confirmed with I-OUS, where it was found that localization was at head of pancreas in two patients, at the tail of pancreas in one patient, at the junction of the corpus-tail of pancreas in one patient and at the corpus of pancreas in two patients. Enucleation was performed in three patients, spleen preserving distal pancreatectomy in one patient and distal pancreatectomy with splenectomy in one patient (Table 1, Figures 3,4).

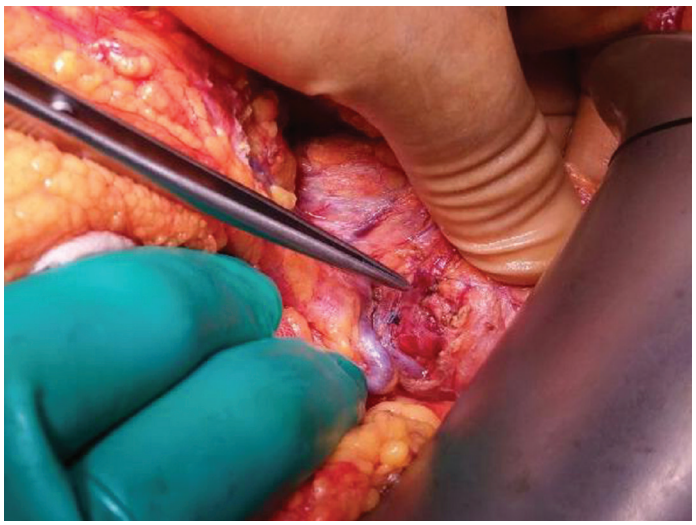

Figure 3. Intraoperative insulinoma

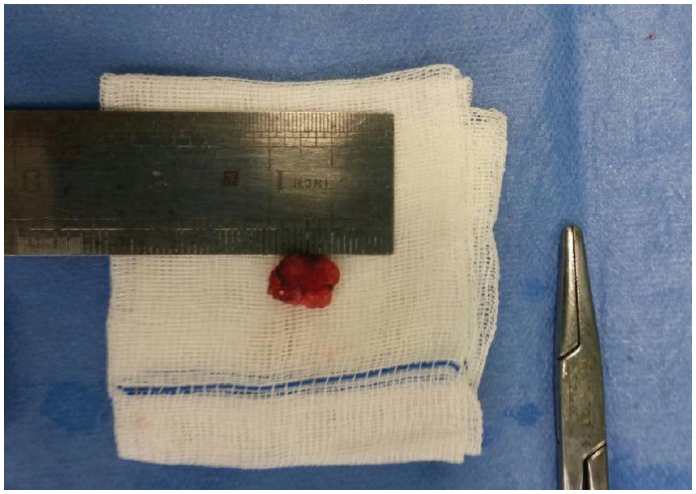

Figure 4. Enucleation specimen

In patients on whom enucleation was performed, insulinoma was detected clearly by both EUS and I-OUS. The other 2 patients, on whom spleen preserving distal pancreatectomy and enucleation were performed, preoperative EUS detected the insulinoma, while I-OUS detected only a suspicion of insulinoma, thereby making it necessary that surgical resection be performed (Figure 3-5).

After enucleation and distal pancreatectomy ± splenectomy, hypoglycemia was not observed during the operation in any of the patients. In postoperative follow up, blood glucose was higher than 100 mg/dl in all patients. On postoperative 1st day, oral fluid feeding was started on the patients. In patient with negative insulinoma (3th patient), the postoperative fasting insulin, HOMA-IR and blood glucose levels were 15.2 uIU/ml (normal range 1.9-23), 5.75 and 109 mg/dl, respectively. Other negative insulinoma patient (5th patient), the postoperative fasting insulin, HOMA-IR and blood glucose levels were 19.4 uIU/ml, 7.2 and 102 mg/dl, respectively. A low-impact pancreatic fistula (< 30 ml drainage) was observed in the 2 patients on whom distal pancreatectomy was performed. Somatostatin analogue was administered to the 2 patients and their nutrition was maintained by total parenteral nutrition. Pancreatic fistula was medically treated for three weeks without ERCP.

Partial wound dehiscence was observed in one patient, but surgical wound care was successfully administered with povidone iodine 10% solution and 0.9% NaCl (Table 2).

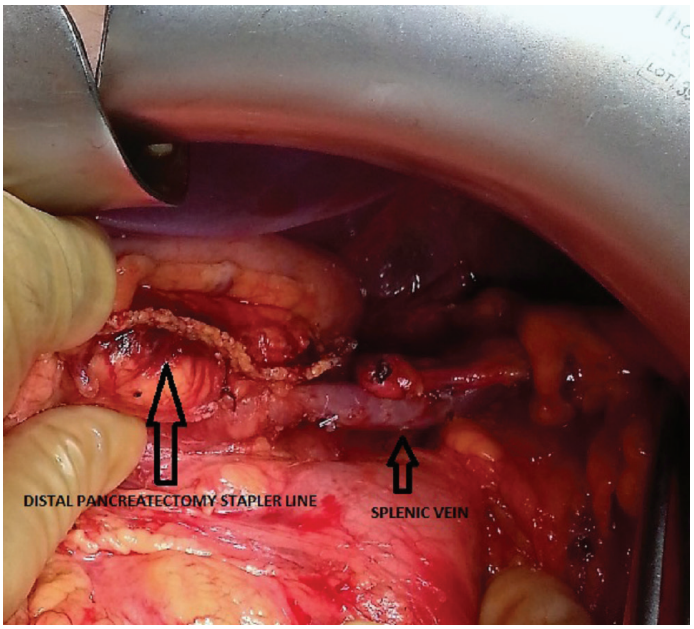

Figure 5. Spleen preserving distal pancreatectomy stapler line

The blood glucose levels of all patients during the postoperative course were detected to be within normal limits. The histopathological examination revealed insulinoma to be present in 3 patients. The Ki-67 proliferation index was measured to be between 2-12%. Granulomatous lymphadenitis was reported in one patient, but neither tuberculosis nor Brucella was found in the follow up after performing detailed research. Medical treatment was administered according to the practices applied by the infectious disease clinic. Finally, in the patient who was reported to have normal pancreas tissue, a histopathological examination was repeated to rule out pancreatic hyperplasia, such as nesidioblastosis. The median length of hospital stay for the five patients was 21 days (min-max: 9-42). The sensitivity and validity of the combined use of EUS and I-OUS were 100% and 60%, respectively, in our study.

Table 2. Postoperative course and complications.

No	Operation	Hospitalization time (days)	Pathology	Ki-67 index (%)	Postoperative hypoglycemia	Re-admission	Complications	Follow up (months)
1	Enucleation	9	Insulinoma	2	No	No	No	6
2	Enucleation	16	Insulinoma	12	No	No	No	10
3	Spleen preserving distal pancreatectomy	21	Pancreatic tissue	No	No	Yes	Pancreatic leak	6
4	Distal pancreatectomy and splenectomy	42	Insulinoma	10	No	No	Pancreatic leak	8
5	Enucleation	24	GL	No	No	No	Partial wound dehiscence	15

GL: Granulomatouslymphadenitis

DISCUSSION

Insulinoma, a benign (> 90%), solitary tumor of the pancreas, and the most common tumor among the islet cell tumors of the pancreas, is an insulin-secreting tumor derived from neoplastic pancreatic islet cells (1,2). The annual incidence of insulinoma is 1/250,000 (2). The etiopathogenesis of this type of tumor is not clear, but it occurs either sporadically or as a component of multiple

endocrine neoplasia type 1 (MEN 1) or of von Hippel-Landau syndrome (3,4). In patients with insulinoma, symptoms and signs are usually associated with hypoglycemia, such as palpitations, tremors, sweating, tachycardia, tachypnea, anxiety, paresthesia, confusion, fainting spells, and dry mouth (4,5). In our patients, these symptoms and signs were observed to be a result of hypoglycemia.

The diagnosis of insulinoma is determined after a supervised 72-hour fasting test, during which the levels of insulin (≥6 μU/ml), C-peptide (≥0.2 nmol/l) and proinsulin (≥5 pmol/l) are measured periodically (6). Preoperative and intraoperative localization of insulinoma is important for the successful management of insulinoma. Both non-invasive and invasive imaging methods, such as abdominal ultrasound (USG), computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy, EUS, I-OUS and trans-hepatic portal venous sampling (THPVS), are often used for the localization of insulinoma (6-8). However, there is no full consensus on which is the best method algorithm for localization of insulinoma (7-8). The sensitivity of the non-invasive imaging methods, CT and MRI, has been reported to be between 33- 64 % and between 40-90 %, respectively (8). Sotoudehmanesh et al. reported the sensitivity of endoscopic ultrasonography for detection of lesions in pancreatic head, body and tail to be 92.6%, 78.9%, and 40.0%, respectively. Invasive modalities have been reported to be higher than non-invasive localization methods (8). Recently, EUS and I-OUS have been increasingly used for the localization of insulinoma. Ersoy et al. and Sotoudehmanesh et al. successfully demonstrated the importance of using EUS and I-OUS together in the diagnosis and treatment of insulinoma (6,8). The effective localization of insulinoma reduces operation time, cuts hospital costs, decreases surgical complications, and results in more successful outcomes. Despite the effective non-invasive and invasive imaging methods, the localization of insulinoma is still often not able to be detected correctly due to an examiner's lack of experience, the isoechoic pattern of insulinoma, and the location and size of the tumor; the sensitivity of these methods is highest for tumors in the head of the pancreas and lowest for those in the tail of the pancreas (7,8). In insulinomas involving the tail and corpus of the pancreas, the effectiveness of EUS, I-OUS and palpation in precisely showing the tumor sometimes fails due to the more problematic anatomic localization and the examiner's lack of experience (8).

Although advanced imaging methods have been developed to ensure operative success in dealing with insulinomas, incidences of failed preoperative localization is still between 10-27% (8,9). In suspected insulinoma patients for whom, due to failed intraoperative palpation and USG, the tumor is not detected, enucleation cannot be performed (10).In these cases, failure to locate the insulinoma is particularly problematic. Hashimato et al. and Dagget et al. suggested that preoperative imaging methods were not necessarily required for localization of insulinoma (11,12). In support of this, the same study by Dagget reported that the combination of surgical exploration and intraoperative USG resulted in the identification of more than 90% of insulinomas (12).

Surgery is the most important curative treatment method for insulinoma, with enucleation being the most common surgical technique. Enucleation is indicated for solitary, small, benign tumors that are able to be clearly detected with preoperative and/or intraoperative imaging methods (9,11,12), but not for tumors involving the pancreatic duct (at least 2-3 mm from the main pancreatic duct). Pancreatic resection is an alternative surgical treatment method. Resection procedures are indicated for malignant

insulinomas where the tumor butts against the pancreatic duct or major vessel, has local adhesion to other tissue or involves the lymph node. Distal pancreatectomy procedures are commonly performed for corpus and tail of the pancreatic insulinoma (13).

However, distal pancreatectomy procedures are associated with higher rates of morbidity and complications, such as high failure rates (> 20%), pancreatic leaks and surgical site infections (14). For these reasons, a blind distal pancreatectomy should be avoided, especially considering the superiority of preoperative imaging methods (6,7,15).

In our study, EUS, I-OUS and palpation were performed to fully detect localization of insulinoma. As both the EUS and the I-OUS showed the insulinoma in 3 patients, enucleation and distal pancreatectomy were performed. On the other hand, in the other 2 patients, EUS showed a pancreatic mass, while I-OUS was only able to slightly detect a pancreatic mass; surgery was therefore performed on these patients. Results from the pathological examinations showed normal pancreatic tissue and granulomatous lymphadenitis in these patients. Postoperative blood glucose was within normal range in these patients.

The patient with granulomatous lymphadenitis received consultation and follow-up care by the infectious disease clinic, while the patient who was found to have normal pancreatic tissue after undergoing a enucleation could have been in the initial stages of insulinoma or hyperplasia, such as nesidioblastosis. In our study, the sensitivity and validity of the combined used of EUS and I-OUS were 100% and 60%, respectively, and these results are similar to those presented in the literature (8,15).

CONCLUSIONS

The combined use of EUS and I-OUS is very important for the localization of insulinoma. It is recommended that distal pancreatectomy and enucleation be performed after complete localization of insulinoma via EUS and I-OUS. However, in light of the prospective randomized studies that have been conducted, for patients who have been clinically diagnosed with insulinoma on the basis of an I-OUS showing suspicion of insulinoma, a distal pancreatectomy should be conducted only after first performing an EUS.

REFERENCES

1. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. World J Gastroenterol 2013;19(6):829-37.
2. Tucker ON, Crotty PL, Conlon KC. The management of insulinoma. Br J Surg 2006;93(3):264-75.
3. Capurso G, Falconi M, Panzuto F, Rinzivillo M, Boninsegna L, Bettini R, et al. Risk factors for sporadic pancreatic endocrine tumors: a case-control study of prospectively evaluated patients. Am J Gastroenterol 2009;104(12):3034-41.
4. Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. Surg Clin North Am 2008;88(4):863-95
5. Whipple AO, Frantz VK. Adenoma of islet cells with hyperinsulinism: a review. Ann Surg 1935;101(6):1299-335.
6. Arslan E, Aziret M, Akgündüz F, İrkörücü O, Reyhan E, Adamhasan F, et al. Importance of together use of endoscopic and intraoperative ultrasonography in the diagnosis and treatment of insulinoma. Int J Basic Clin Med 2016;4(2):74-8.
7. Goh BK, Ooi LL, Cheow PC, Tan YM, Ong HS, Chung YF, et al. Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. J Gastrointest Surg 2009;13(6):1071-7.
8. Sotoudehmanesh R, Hedayat A, Shirazian N, Shahraeeni S, Ainechi S, Zeinali F, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine 2007;31(3):238-41
9. Grant CS. Gastrointestinal endocrine tumours. Insulinoma. Baillieres Clin Gastroenterol 1996;10(4):645-71.
10. Zhao YP, Zhan HX, Zhang TP, Cong L, Dai MH, Liao Q, et al. Surgical management of patients with insulinomas: result of 292 cases in a single institution. J of Surg Oncol 2011;103(2):169-74.
11. Hashimoto LA, Walsh RM. Preoperative localization of insulinomas is not necessary. J Am Col lSurg 1999;189(4): 368-73.
12. Daggett PR, Goodburn EA, Kurtz AB, Le Quesne LP, Morris DV, Nabarro JD, et al. Is preoperative localisation of insulinomas necessary? Lancet 1981;1(8218):483-6.
13. Ravi K, Britton BJ. Surgical approach to insulinomas: are preoperative localisation tests necessary? Ann R Coll Surg Engl 2007;89(3):212-7.
14. Hirshberg B, Libutti SK, Alexander HR, Bartlett DL, Cochran C, Livi A, et al. Blind distal pancreatectomy for occult insulinoma, an inadvisable procedure. J Am Col lSurg 2002;194(6):761-4.
15. Davi MV, Falconi M. Pancreas: Insulinoma--new insights into an old disease. Nat Rev Endocrinol 2009;5(6):300-2.