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The Role of Endoscopic Ultrasonography for Localization of Insulinomas without a Pancreatic Lesion on Magnetic Resonance Imaging: A Short Series and Literature Review

Manyetik Rezonans Görüntülemede Pankresta Lezyon Saptanmayan Insülinomaların Lokalizasyonunda Endoskopik Ultrasonografinin Rolü: Olgu Serisi ve Literatür Derlemesi

Sayid Shafi Zuhur, İdris Kuzu*, Feyza Yener Öztürk*, Sibel Erdamar**, Yüksel Altuntaş*

Namık Kemal University Faculty of Medicine, Department of Endocrinology and Metabolism, Tekirdağ, Turkey
*Şişli Etfal Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Turkey
**İstanbul University Cerrahpaşa Faculty of Medicine, Department of Pathology, İstanbul, Turkey

Abstract

Insulinoma is a rare neuroendocrine tumor of the pancreas and is the most common cause of endogenous hyperinsulinemic hypoglycemia. Although 90% of insulinomas are benign tumors, recurrent episodes of hypoglycemia may lead to life-threatening consequences. Since surgery is the only curative method for patients with insulinomas, the preoperative localization of these tumors by appropriate imaging methods is important. In this case series, we report 5 patients with endogenous hyperinsulinemic hypoglycemia, including one with MEN-1 syndrome, who were diagnosed with insulinoma according to the prolonged fasting test. All patients had normal pancreas on upper abdominal magnetic resonance imaging (MRI), therefore, they underwent endoscopic ultrasonography (EUS) for localization of the insulinomas and were operated according to the EUS results. EUS demonstrated well-demarcated tumors in the tail of the pancreas in 4 subjects and in the head of the pancreas in one patient. However, in contrast to EUS results, one patient with MEN-1 syndrome had a glucagonoma and two insulinomas and one patient had not any tumor on histopathological evaluation of the distal pancreas after surgery. In this case series, we aimed to present the diagnostic performance of EUS and the treatment outcomes in a cluster of patients with insulinomas who had not a pancreatic lesion on upper abdominal MRI and to briefly review the currently available imaging methods for localization of insulinomas. *Turk Jem 2015; 19: 93-98*
Key words: Insulinoma, MEN-1 syndrome, sporadic, endoscopic ultrasonography

Özet

İnsülinoma pankreasın nadir rastlanan bir endokrin tümörü olup endojen hiperinsülinemik hipogliseminin en yaygın sebebidir. insülinomaların %90'ı benign tümörler olmalarına rağmen, tekrarlayan hipoglisemi epizodları yaşamı tehdit edici sonuçlara yol açabilir. Cerrahinin insülinomalı hastalar için tek küratif tedavi metodu olmasından dolayı, uygun görüntüleme metodlarıyla bu tümörlerin preoperatif lokalizasyonu önemlidir. Bu olgu serisinde biri MEN-1 sendromlu bir olgu olmak üzere, uzamış açlık testine göre insülinoma tanısı alan, endojen hiperinsülinemik hipoglisemili 5 olgu sunulmuştur. Bütün olgularda pankreas üst abdomen Manyetik Rezonans (MR) normal saptandığından insülinomanın lokalizasyonu için endoskopik ultrasonografi (EUS) yapıldı ve EUS sonuçlarına göre ameliyat edildiler. EUS bir olguda pankreasın başında ve 4 olguda ise pankreasın kuyruğunda sınırları belirgin olan tümörlerin varlığını saptadı. Ancak EUS sonuçlarının aksine cerrahiden sonra distal pankreasın histopatolojik incelemesinde, MEN-1 sendromlu bir hastada bir glukagonoma ile birlikte iki insülinoma saptanırken diğer bir hastada ise herhangi bir tümör saptanmadı. Bu olgu serisinde, üst abdomen MR'ında pankreatik lezyonu saptanmayan insülinomalı bir hasta grubunda EUS'un diagnostik performansı ile takip ve tedavi sonuçlarını sunmayı ve insülinomaların lokalizasyonu için günümüzde kullanılan görüntüleme metodlarını kısaca gözden geçirmeyi amaçladık. *Turk Jem 2015; 19: 93-98*
Anahtar kelimeler: İnsülinoma, MEN-1 sendromu, sporadik, endoskopik ultrasonografi

Address for Correspondence: Sayid Shafi Zuhur MD, Namık Kemal University Faculty of Medicine, Department of Endocrinology and Metabolism, Tekirdağ, Turkey
Phone: +90 542 612 60 29 E-mail: zuhur744@gmail.com **Received:** 30/01/2015 **Accepted:** 05/04/2015

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Introduction

Insulinoma is a rare neuroendocrine tumor (NET) of the pancreas with an incidence of 1-4 cases per million population (1). These tumors are generally sporadic, solitary and less than 2 cm in diameter. However, approximately 10% of cases may be a part of multiple endocrine neoplasia type-1 syndrome (MEN-1 syndrome) in which the insulinomas are generally multifocal (1). Although 90% of these tumors are benign (1), recurrent episodes of hypoglycemia may lead to life-threatening consequences. Therefore, the appropriate diagnosis, localization and treatment of these tumors are of paramount importance.

The diagnosis of insulinomas often requires a two-stage process. The first stage is the biochemical proof of the endogenous hyperinsulinemic hypoglycemia along with the exclusion of other causes of hypoglycemia and, the second stage involves the localization of the tumor by appropriate imaging methods. Surgical treatment is the only curative method and generally accomplished with tumor enucleation or partial resection of the pancreas (2). Pre-operative localization of insulinomas is the most important predictor of surgical outcome and the possibility of surgical failure is quite high in cases that are not well localized pre-operatively. However, despite of the significant improvement in non-invasive and invasive imaging methods, a considerable number of insulinomas could not be localized pre-operatively and the management of such cases creates significant difficulties for endocrinologists and surgeons. Herein, we present 5 cases of patients with insulinoma who had not any pancreatic tumor on gadolinium-enhanced upper abdominal magnetic resonance imaging (MRI) but had pancreatic tumors on endoscopic ultrasonography (EUS) and were operated according to the EUS results. We also briefly discuss the imaging modalities currently used for localization of insulinomas.

Methods

Five patients with documented Whipple's triad witnessed by a physician who were diagnosed as having insulinoma according to the results of 72-hour fasting test between 2009 and 2012 in our center were included in this study. Comorbidities, including congestive heart failure, chronic kidney and liver diseases as well as adrenal insufficiency were excluded by history, physical examination and appropriate laboratory tests. All patients were also screened for multiple endocrine neoplasia type-1 syndrome (MEN-1 syndrome) by appropriate biochemical tests. The family history was negative for NET, primary hyperparathyroidism and pituitary tumors in all patients including one case of MEN-1 syndrome.

Seventy-two-hour fasting test and diagnostic criteria: All the patients were hospitalized at least 3 days before 72-hour fasting test was started and the test was started at early morning in all patients. Venouse blood samples for glucose, C-peptide and insulin were collected every six hour and during symptomatic hypoglycemia (<55 mg/dl). Biochemical diagnosis of insulinoma was established in patients with a high C-peptide (≥0.6 ng/ml) and insulin (≥3 μU/ml) levels when hypoglycemia (<55 mg/dl) was established (3). Insulin antibodies were negative in all subjects. However, because plasma or urine sulfunylurea levels could not be assessed at that time in our center, all patients were hospitalized at least three days before 72-hour fasting test to observe for surreptitious consumption of sulfunylureas and meglitinides. Symptomatic hypoglycemia was detected 6, 9, 16, 22 and 30 hours after the start of the 72-hour fasting test in cases 1, 2, 3, 4 and 5 respectively.

Abdominal imaging: All patients underwent gadolinum-enhanced upper abdominal MRI at some point prior to EUS. The pancreas was normal on upper abdominal MRI images in all patients.

EUS: All EUS examinations were performed by experienced gastroenterologists after an overnight fast in left lateral decubitus position and under intravenous sedation. Fine needle aspiration (FNA) was performed during EUS by using a 22-gauge shot gun aspiration in all subjects.

Since gadolinium-enhanced upper abdominal MRI did not show a pancreatic mass lesion in any case and intra-arterial calcium stimulation test with hepatic venous sampling (ASVS) could not be performed, all patients underwent surgery, according to the EUS results.

Clinical Data and Treatment Outcomes

Case 1: Was a 27-year-old female patient. She presented with palpitation, sweating, lightheadedness and slurred speach, usually occurring at early mornings. She had experienced 3 episodes of syncope in the past one year and hypoglycemia had been detected during investigation for neurological pathologies. She also reported a recent 7 kg weight gain. Primary hyperparathyroidism was found on biochemical evaluations and a pituitary tumor sized 4 mm in diameter was also found on pituitary MRI which was non-functional on hormonal studies. The patient was diagnosed as having MEN-1 syndrome. EUS demonstrated a 9x7 mm well-circumscribed hypo-echoic tumor in the tail of the pancreas. Histopathological evaluation of the FNA material demonstrated strong positivity for chromogranin and was consistent with NET. Technetium-99 m sestamibi + positron emission tomography (PET)/ computed tomography (CT) displayed a high uptake of radiotracer in the anterior side of C7 vertebrae, consistent with ectopic parathyroid adenoma. The patient underwent distal pancreatectomy. In contrast to the EUS result, three distinct tumors (0.8x0.6 mm; 0.6x0.6 mm and 0.x0.4 mm) were found on histopathological evaluation of the distal pancreas. The largest tumor sections were strongly positive for glucagon and chromogranin and negative for insulin and somatostatin and the other 2 tumor sections were strongly positive for insulin and negative for glucagon and somatostatin (Figure 1). All the 3 tumors displayed a Ki-67 labeling index (LI) of less than <1%. The patient also underwent parathyroid surgery and a parathyroid adenoma was found inside the thymus gland. However, hypoglycemia did not improve after surgery. Repeated MRI, EUS and somatostatin receptor scintigraphy (SRS) failed to show any tumor in the pancreas or other parts of the abdomen. The patient refused any further surgery. Medical treatment with diazoxide was started and she remains euglycemic under tretment with diazoxide 4 years

after her operation. The patient and her family refused genetic analysis for MEN-1 syndrome.

Case 2: Was a 31-year-old female patient. She presented with episodes of excessive sweating, termor, palpitation, blurred vision and anxiety, occurring generally several times during the day, after short periods of fasting. She also reported a recent 14 kg weight gain. EUS demonstrated a 15x12 mm well-circumscribed hypo-echoic tumor in the tail of the pancreas (Figure 2). FNA material was non-diagnostic on histopathological evaluation. Distal pancreactectomy was performed according to the EUS findings and palpation of the pancreas during surgery, however, neither a tumor nor β cell hyperplasia was found on histopathological evaluation of the distal pancreas. Symptomatic hypoglycemia continued after distal pancreatectomy. Repeated gadolinium-enhanced upper abdominal MRI, EUS and SRS failed to show any lesion in the pancreas or other parts of the abdomen. She also refused further surgery. Medical treatment with diazoxide was started but the patient was not well-controlled with medication. Albeit infrequent, some episodes of moderate to severe hypoglycemia were occured in the first postoperative year. However, the patient lost to follow-up after one year.

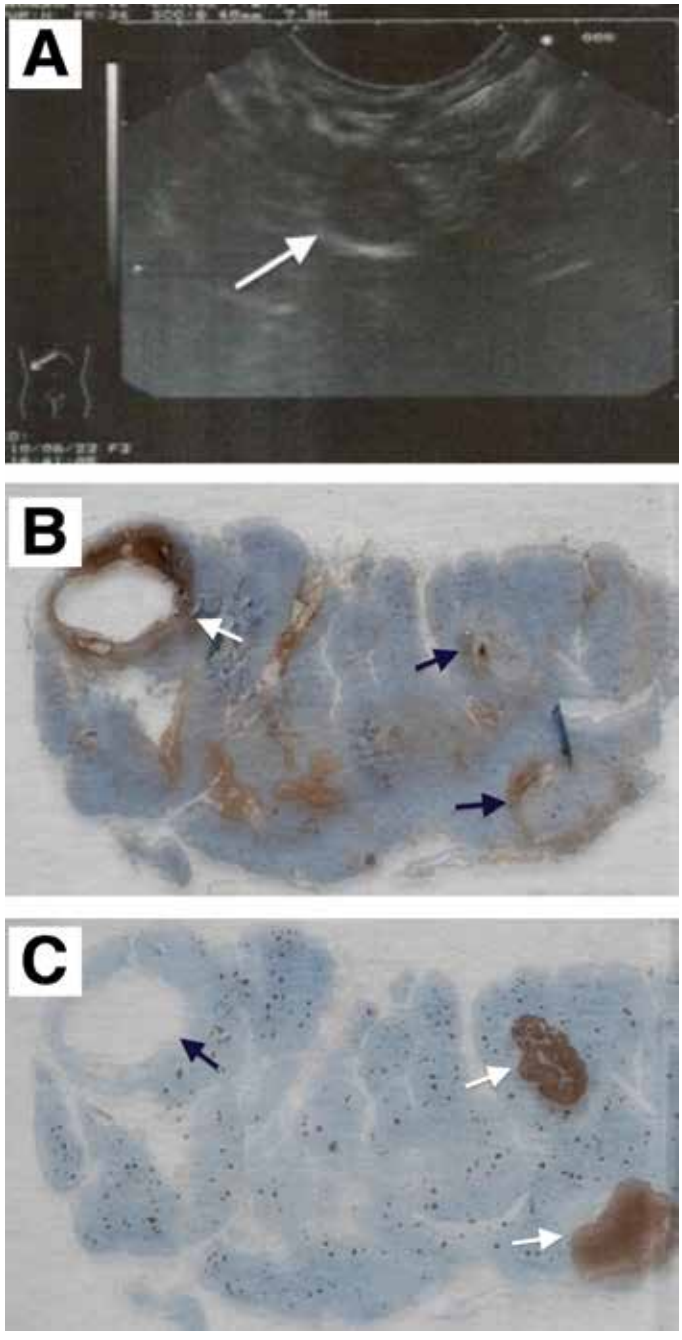

Figure 1. A) Endoscopic ultrasonography image of the patient in case 1 displays only one well-demarcated tumor in the tail of pancreas, B) Immunostaining for glucagon depicts a glucagonoma (white arrow). Two insulinomas appear negative for glucagon (black arrows), C) Immunostaining for insulin depicts two small insulinomas (white arrows) in distal pancreas section of the same patient and the glucagonoma appears negative for insulin (black arrow)

Case 3: Was a 44-year-old female patient. She presented with anxiety, excessive sweating and tremor, usually occurring during prolonged fasting. She also reported weight gain but she did not know how much was her actual weight before her complaints have started. EUS demonstrated a well-demarcated hypo-echoic mass measuring 12x9 mm at the head of pancreas, but FNA was non-diagnostic. The patient underwent surgery and enucleation of the tumor was performed. The histopathological evaluation of the tumor sections was strongly positive for insulin and chromogranin and the Ki-67 LI was less than 1%. The patient remains euglycemic and free of symptoms 4 years after her operation.

Case 4: Was a 27-year-old female patient. She was referred from the emergency service of our center. She was transferred to the emergency service due to syncope without complete loss of conscious and hypoglycemia was established during laboratory evaluations at the emergency department. The patient reported that she had experienced several episodes of syncope at early mornings during last 6 months, but of lesser severity. She also reported sweating, tremor and palpitation during fasting and a recent 15 kg weight gain. EUS demonstrated a well-circumscribed 12x10 mm hypo-echoic lesion in the tail of the pancreas. The histopathological evaluation of FNA of the tumor was consistent with NET (Figure 3). Distal pancreatectomy was performed and histopthological evaluation demonstrated 13x12 mm tumor with

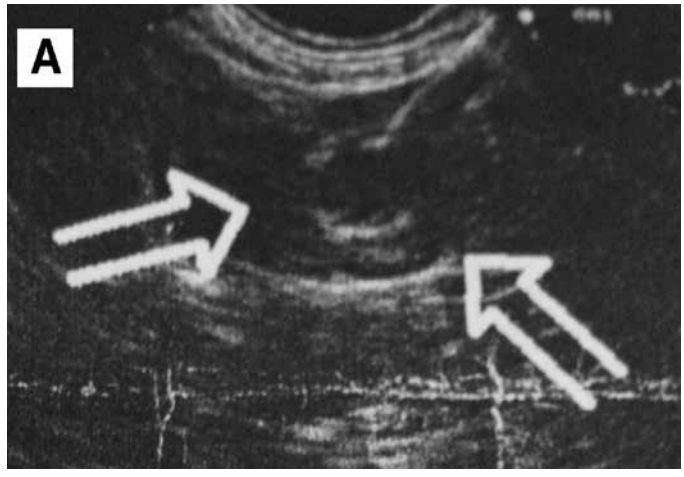

Figure 2. The endoscopic ultrasonography image of the patient in case 2 displays a well-demarcated tumor in the tail of pancreas

strong positivity for insulin and chromogranin. Ki-67 LI was less than 1%. The patient remains euglycemic and free of symptoms 3 years after her operation.

Case 5: Was a 45-year-old female patient. She presented with excessive sweating, palpitation, tremor and temporary diplopia, usually occurring during early mornings and before dinner. She also reported a recent weight gain of 19 kg. EUS showed a well-demarcated, round, 7x6 mm hypo-echoic lesion in the tail of the pancreas. FNA was non-diagnostic. The patient underwent distal pancreatectomy. The histopathological evaluation demonstrated an 8x9 mm tumor strongly positive for insulin and chromogranin. Ki-67 LI was negative. The patient remains euglycemic and free of symptoms 5 years after her operation.

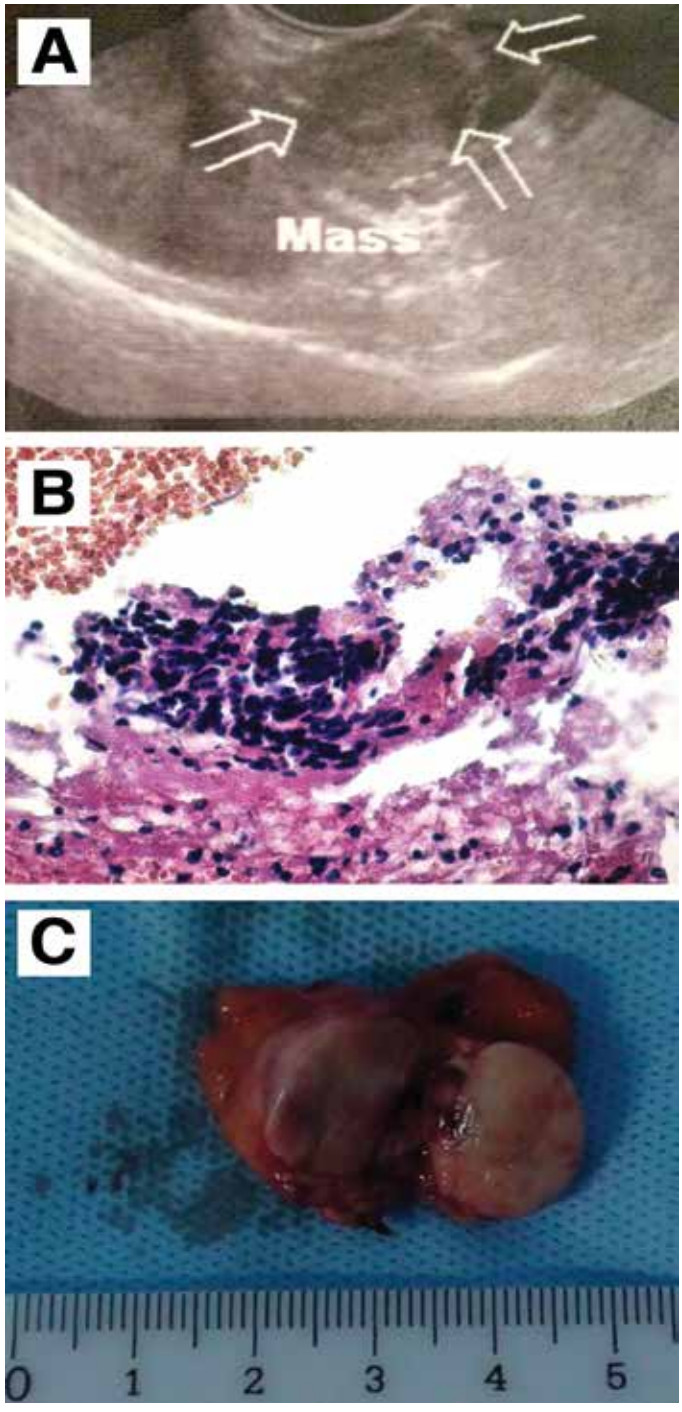

Figure 3. A) Endoscopic ultrasonography image of the patient in case 4 displays a well-demarcated tumor in the tail of pancreas, B) Haematoxylin&eosin staining of the fine needle aspiration biopsy material of the tumor displays neuroendocrine cells (BX40), C) An insulinoma in the tail of pancreas of the patient presented in case 4

Discussion

Insulinomas are the most common cause of endogenous hypoglycemia. Therefore, in a non-diabetic patient with fasting and/or postprandial hypoglycemia, insulinoma should always be considered in differential diagnosis. The symptoms of insulinoma are the same as the other causes of hypoglycemia and consist of autonomic symptoms including palpitation, excessive sweating, tremor, anxiety, feel of hunger, dry mouth and neuroglycopenic symptoms including slurred speach, blurred vision, diplopia, personality and behavioral changes, seizure, confusion, and coma (4).

According to the recent classification of the World Health Organization (WHO), NETs araising from the pancreas or other parts of the gastrointestinal tract are histopathologically divided into grade I, II and neuroendocrine carcinoma. This classification is made according to the level of mitosis and Ki-67 LI (5). Thus, in our case series, except for case 2, all other tumors were grade I NETs (5).

Most of insulinomas are sporadic and less than 2 cm in diameter (1,6), therefore, the preoperative localization of insulinomas may fail by using noninvasive imaging methods, including trans-abdominal USG, CT and MRI. Therefore, invasive imaging methods are often required for precise localization of these tumors.

One of the widely used imaging methods for the diagnosis of intra-abdominal pathologies is trans-abdominal USG. However, trans-abdominal USG is generally not effective for identification of insulinomas, because most of insulinomas are of small size and the gas overlying the pancreas can make visualization of the pancreas difficult. The sensitivity of trans-abdominal USG is ranging between 9% and 64% for localization of insulinomas (4,7). Therefore, unlike other intra-abdominal pathologies, nowadays, USG is not used as the first-line imaging method for localization of insulinomas. Trans-abdominal USG was performed in all of the cases presented here, before upper abdominal MRI and the results were also negative in all cases.

CT is currently used as the first-line imaging method for the diagnosis of insulinomas in most countries (4). It is less expensive, non-invasive and a simple method for the diagnosis of insulinomas. According to studies, the sensitivity of CT ranges between 39% and 75% for localization of insulinomas (8). However, technical progression has improved the quality of CT. In a recent study, the sensitivity of multidetector CT for identification of insulinomas was reported to be 94.4% (9). Typically, insulinomas appear as hypervascular tumors on CT and demonstrate higher degree of enhancement than surrounding paranchyma. MR is another safe and non-invasive method for visualization of insulinomas and its sensitivity is better than CT for identification of insulinomas (10). Insulinomas generally show a low signal intensity on T1-weighted and high signal intensity on T2-weighted

imagings, they also typically demonstrate a strong enhancement in the arterial phase and a prolonged enhancement compared to the normal pancreas parenchyma in delayed phase (11,12). MRI is often used as the first-line diagnostic method for localization of insulinomas in our country, perhaps due to its high quality outcomes in soft tissue imaging and due to its wide availability. Therefore, gadolinium-enhanced MRI was performed in all of our cases and like trans-abdominal USG the results were negative in all cases. One possible explanation for the negative MRI results is the small size of the tumors in all cases. However, some insulinomas contain large amount of fibrosis, this fibrosis may reduce blood-flow by compressing the arterial supply and may result in reduced tumor enhancement (13,14), and in this way, may lead to false negative results.

In recent years, EUS has become the most preferred imaging method for preoperative localization of insulinomas not detected by conventional non-invasive imaging methods. Insulinomas are generally seen as well-demarcated hypo-echoic tumors on EUS. In a study by Rösch et al., the sensitivity and specificity of EUS for localization of endocrine pancreatic tumors were 82% and 95%, respectively (15). Recent studies comparing EUS with helical CT, MRI and PET have found EUS to have a higher sensitivity for identification of pancreatic tumors (16). Besides good sensitivity, EUS also provides the ability to perform FNA. However, studies suggest a lower sensitivity of EUS for detection of lesions in the tail of the pancreas where the sensitivity is between 50% and 60% as compared with 95% and 98% for the tumors located in the head and body of the pancreas, respectively (17). This is the anatomic disadvantage of EUS and reflecting the difficulty in scanning of the tail of the pancreas from stomach, particularly in subjects with high retroperitoneal fat content (17). In a recent retrospective study, Kann et al. (18) evaluated the factors associated with negative EUS imaging in patients with insulinoma. Of the 29 cases evaluated in their study, 3 tumors were not detected preoperatively and all of these tumors were suggested to be iso-echoic on EUS. They found that female gender, low body mass index and young age were associated with negative EUS imaging. Schumacher et al. (19) suggested that the presence of peripancreatic lymph nodes may cause false-positive results during EUS examination of insulinomas. The EUS result was falsely positive in one of the cases presented here, however, upper abdominal MRI did not show the presence of any peripancreatic lymph node in that patient. EUS also showed only one tumor in case 1, however, three distinct tumors were found on histopathological evaluation of the distal pancreas. This result demonstrates that EUS may also miss some small tumors of the pancreas. Like other invasive imaging procedures, EUS also has some other shortcomings including lack of universal availability, requirement of sedation, operator dependence and invasiveness. As demonstrated in case 1, pancreatic NETs are generally multifocal in patients with MEN-1 disease, therefore, in patients with MEN-1 syndrome, surgery should not be performed based on the results of EUS alone and, if possible, a combination of localaization procedures including ASVS and intraoperative ultrasonography (IOUSG) should be performed for precise localization of insulinomas in these patients. Likewise, as reported by several studies and was also shown in the first and second cases of this report, EUS has not enough sensitivity to identiy insulinomas located in the tail of the pancreas, therefore, the presence of the tumor should be confirmed before or during surgery by other diagnostic methods, to avoid blind distal pancreatectomy.

Another ultrsonographic method used for localization of insulinomas is IOUSG. Although there is not any study to compare the sensitivity between IOUSG and other imaging techniques and most of the papers are confined to case reports, IOUSG can identify most of the tumors that are not detected by other pre-operative localization methods. Studies reported a sensitivity of 80-100% for IOUGS (20,21). However, as 10% of insulinomas are iso-echoic on USG, a significant percentage of the cases may also be missed by IOUSG (22).

ASVS is used since 1998 for localization of insulinomas which were not detected by other pre-operative imaging procedures. This method has a sensitivity of 96% for localization of insulinomas (23). However, even in experienced centers, a respective false-negative and false-positive results were reported in 11% and 4% of the cases underwent this localization procedure (24). Despite its unavailability in most of the centers, especially in our country, and a considerable rate of false-negative and false-positive results, nowadays, this test is considered the most sensitive procedure for localization of insulinomas not detected by other pre-operative localization procedures.

Functional imaging methods using different radioisotopes are also used for pre-operative localization of insulinomas. One of the widely used functional imaging methods for localization of gastroenteropancreatic NETs is SRS. However, unlike other gastroenteropancreatic NET, somatostatin receptor expression is low in insulinomas, thus, the detection rate of insulinomas with SRS is very low (8) and the sensitivity of this method is less than 50% for localization of insulinomas. In our patients, SRS was performed after failure of surgery in cases 1 and 2, however, SRS was also negative in both cases. Our results are in line with what is reported in other studies and demonstrates the low diagnostic performance of SRS for localization of insulinomas. Recently, 68Ga DOTATATE PET/CT and 111In-DTPA-exendin-4 SPECT/CT were demonstrated to be effective for localization of some cases of insulinomas not localized by SRS (8,25). However, these radioisotopes are highly expensive and are not currently available in our country.

In conclusion, several invasive and non-invasive imaging methods with different sensitivities are present for pre-operative localization of insulinomas. However, as discussed above, each of these methods has its own advantages and disadvantages. Therefore, several factors, including the size of the tumor, the localization of the tumor in the pancreas, the genetic basis of the tumor and the experience of the operator in operator-dependent procedures should be taken in consideration when interpreting the imaging studies, and if possible, the presence and localization of the tumor shoud be confirmed also by a second imaging method to avoid false diagnosis. Particular attention should be paid when EUS displays a mass in the tail of the pancreas, particularly in a patient with MEN-1 syndrome in which case the insulinomas may be multifocal.

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Concept: Sayid Shafi Zuhur, Yüksel Altuntaş, **Design:** Sayid Shafi Zuhur, Yüksel Altuntaş, **Data Collection or Processing:** İdris Kuzu, Feyza Yener Öztürk, **Analysis or Interpretation:** Sibel Erdamar, Yüksel Altuntaş, **Literature Search:** Sayid Shafi Zuhur, İdris Kuzu, **Writing:** Sayid Shafi Zuhur, **Peer-review:** Externally peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors, **Financial Disclosure:** The authors declared that this study has received no financial support.

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