 Contrast-Enhanced Endoscopic Ultrasonography Improves the Preoperative Localization of Insulinomas

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Abstract. We report a case in which endoscopic ultrasonography (EUS), intraductal ultrasonography (IDUS) and contrast-enhanced EUS using Levovist helped to localize insulinoma correctly. A 74-year-old woman complained of symptomatic fasting hypoglycemia with relatively high concentration of serum insulin level. Dynamic contrast-enhanced computed tomography revealed a small tumor of 8 mm diameter in the pancreatic head. Insulin secretion was strongly stimulated by calcium injection into the gastroduodenal artery. To clarify the precise localization, we performed EUS, IDUS and contrast-enhanced EUS. The tumor was enhanced clearly by Levovist, and the distance from the main pancreatic duct was more than 3 mm. Therefore, a preoperative decision could be made to use the enucleation method for resection of the tumor. The surgeon could enucleate the tumor in a brief operation according to the preoperative diagnosis, and serum glucose levels returned to normal range after the operation. Contrast-enhanced EUS using Levovist was shown to be a useful diagnostic method for precise localization of small insulinoma.

Key words: Insulinoma, Endoscopic Ultrasonography, Intraductal ultrasonography, Levovist

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INSULINOMA is the most common endocrine tumor in pancreas [1]. Patients with insulinoma usually show symptomatic fasting hypoglycemia with relatively high level of serum insulin. The diagnosis and preoperative localization of insulinomas are difficult in some cases. Selective arterial calcium stimulation and hepatic venous sampling (ASVS) is a very sensitive technique for diagnosis and localization of insulinomas [2, 3], while the procedure is not perfect for the precise and accurate localization of tumor in the pancreas yet. Although intraoperative ultrasonography (US) is also very useful for the final diagnosis, the technique will miss some insulinomas [4-7]. In recent studies, preoperative endoscopic ultrasonography (EUS) has been shown to have a higher sensitivity for localizing insulinomas (70-83.3%) than either transabdominal US, computed tomography (CT), or magnetic resonance imaging (MRI) [8, 9]. Somatostatin receptor scintigraphy (SRS) using 111In-pentetetocide is also a new noninvasive imaging method for detecting gastrointestinal neuroendocrine tumor. However, the sensitivity for diagnosing insulinoma (60%) [10] is less than that of EUS. Intraductal ultrasonography (IDUS) has also been shown to precisely detect the localization of small insulinomas [11].

Leovist (SH U 508A; Schering, Berlin, Germany)
is the first microbubble agent to produce reliable and clinically useful systemic Doppler enhancement after intravenous injection during US [12]. We have also reported that the contrast-enhanced IDUS using Levovist is useful for the diagnosis of bile duct diseases [13, 14]. In this report, we present a case in which EUS, IDUS and contrast-enhanced EUS helped to localize insulinoma correctly.

Case Report

A 74-year-old woman diagnosed with right ovarian cancer was admitted to our hospital for the removal of tumor. Optimal resection for the cancer was performed in our department of gynecology. Before the operation, she often showed symptomatic fasting hypoglycemia usually in the morning. Those hypoglycemic episodes continued after the surgery and she was given continuous intravenous infusion of glucose solution every day to adjust blood glucose level. Her plasma glucose levels were often below 2.8 mmol/L (50 mg/dl), and insulin concentration was 2.9 μU/ml when plasma glucose was 2.4 mmol/L (43 mg/dl). She also showed a relatively high concentration of serum c-peptide of 4.44 ng/ml when her insulin level was 9.7 μU/ml and plasma glucose was 4.4 mmol/L. Fajans index (serum insulin/plasma glucose) of this patient (2.9/43 = 0.067) was lower than diagnostic level (0.3) [15]. However, recent enzyme immunoassays for insulin specifically measure the serum insulin level without cross-reaction for c-peptide, in which case Fajans index of some cases of insulinoma is lower than 0.3. Therefore, insulinoma should be suspected when the patient presents Whipple’s triad (low blood glucose, symptoms of hypoglycemia, relief by food) together with detectable serum insulin level during symptomatic hypoglycemia. We ruled out other causes of hypoglycemia, including hypopituitarism, hypoadrenocorticism and hypothyroidism. Dynamic contrast-enhanced CT revealed a small tumor of 8 mm diameter in the pancreatic head (Fig. 1). We performed ASVS for the functional diagnosis and to confirm the localization of the tumor. A dose of 0.025 mEq/kg calcium gluconate was injected into the superior mesenteric (SMA), splenic (SA), hepatic (HA), dorsal pancreatic (DPA) and gastroduodenal (GDA) arteries. Blood samples were obtained from the right hepatic vein at 0, 30, 60 and 180 s after calcium injection. Insulin secretion was strongly stimulated by calcium injection into the gastroduodenal artery (Fig. 2). Arterial phases of a gastroduodenal artery angiogram showed a small, hypervascular, and well-circumscribed tumor in the pancreatic head (Fig. 3). The tumor was localized near the pancreatic duct in the dynamic CT scan. Pancreatoduodenectomy is considered to be necessary to resect insulinomas located within 2-3 mm from the main pancreatic duct. To measure the precise distance between the tumor margin and the main pancreatic duct, we performed EUS and IDUS. These ultrasound examinations were carried out with
Fig. 3. Arterial phase of a hepatic artery angiogram. A small, hypervascular and well-circumscribed insulinoma (arrowhead) is vasculized from a gastroduodenal artery (arrow).

Fig. 4. EUS image revealed an insulinoma with marginally hypoecholic lesion in the pancreatic head (arrow in A). IDUS presents more precise localization of the hypoecholic tumor (arrow in C). The tumor is clearly enhanced by Levovist (arrows in B and D), and the distance from the main pancreatic duct is more than 3 mm (broad arrow in C and D). Scale bars (white lines) in A and B are 8 mm, and those in C and D are 4 mm.
Figure 5. Hematoxylin-eosin and immunohistochemical stainings of tumor sections. Hematoxylin-eosin stained section of tumor reveals typical neuroendocrine features. Islet-like clusters of uniform-appearing small cells with central nuclei containing finely dispersed chromatin can be seen (A). Immunohistochemical stainings of chromogranin A (B) and insulin (C) of the sequential sections showed neuroendocrine cells and insulin secreting cells, respectively.

Discussion

A combination of intraoperative palpation and intraoperative US is the most sensitive method to localize insulinomas [4-7]. However, this method prolongs surgery and has an associated risk of rupture of the splenic vessels due to mobilization of the pancreas [16, 17]. Therefore, precise preoperative localization of insulinomas and assessment of malignancy with or without metastasis are essential [18, 19]. Although, transabdominal US, CT, MRI, angiography and ASVS are currently used to localize insulinomas, about 40% or more of all pancreatic adenomas, including insulinomas, miss being detected by these preoperative diagnostic methods [16, 20-24].

EUS is a sensitive method for diagnosing small pancreatic carcinomas [25] and insulinomas [26-29]. In a recent report, the sensitivity of EUS for localizing insulinomas was estimated as 90% [18]. In the past several years, IDUS has been developed for the diagnosis of choledochocolic and pancreatic carcinoma. IDUS is also a highly sensitive diagnostic procedure for localizing very small insulinomas in the pancreatic head [11]. IDUS using an ultrasound frequency of 20 MHz has higher resolution than that of EUS. Then the detection rates of EUS and IDUS to find small masses (1-3 mm in diameter) in the cyst
were 20 to 30% and more than 90%, respectively [30]. In parallel with the development of the US procedures, various agents have been investigated for use in effective enhancement by ultrasound. Levovist is one of the clinically available microbubble agents for such enhancement, and consists of galactose microaggregates (99.9%) with a small admixture of palmitic acid (0.1%). When it is mixed with water, agitated, and allowed to stand for 2 min, multiple small stabilized air microbubbles with a mean diameter of 1-2 μm are produced. These are sufficiently small and stable to pass repeatedly through capillary beds and thereby provide useful systemic enhancement after intravenous injection. Levovist has been demonstrated to have excellent tolerance and safety, with only minor adverse reactions reported [12]. In the present case, the tumor had a diameter of 8 mm, and was well enhanced in dynamic CT. However, the very small insulinoma is not detected by this method. Although the conventional EUS or IDUS examinations sometimes reveal a tiny tumor as a hypoechoic mass lesion, the enhancement by Levovist improves the ultrasound image of hypervascular endocrine tumors such as insulinoma. We easily detected the location of the tumor and measured the distance between the pancreatic main duct and tumor margin. In this case, the distance was more than 3 mm, and enucleation of the tumor was recommended before surgery. The surgeons thus obtained information about the location of the insulinoma preoperatively, and were able to enucleate the tumor successfully in a brief surgery without intraoperative US or other additional diagnostic maneuvers. Short time operation and minimal diagnostic and surgical stress on the pancreas is beneficial to the patient’s prognosis.

In the present study, we reported a case of insulinoma in which precise localization of the tumor was performed by contrast-enhanced EUS and IDUS. The methods are useful to clarify the localization of small endocrine tumors in pancreas, and the preoperative diagnosis improves the surgical procedure.

References