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Case Report
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Endoscopic Ultrasound - Guided Ethanol Injection for Pancreatic Insulinoma

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Abstract

Pancreatic insulinoma is the most common neuroendocrine tumor of pancreas expressing hormonal manifestation. While majority of insulinoma is benign, complete resection of tumor with enucleation already provided potential cure. Ff tumor is located at head of pancreas and close proximity to main pancreatic or common bile duct, enucleation often lead to pancreatic leakage and morbidity. However, major pancreatectomy including Whipple operation is also major undertaking. Endoscopic ultrasound guided alcohol injection with ablative effect offers an alternative for treatment of pancreatic insulinoma with low morbidity. In this report, we will share our experience and review the current literature on EUS-guided alcohol ablation for pancreatic fistula.

Case Presentation

A 75-year old woman was admitted to hospital through causality because of dizziness and syncope. She was found to be hypoglycemic with Histix of 2.7. She had hypertension for 20 years, and follicular thyroid carcinoma with bone metastasis, treated with total thyroidectomy and radio-ablative iodine 6 months ago. There was no history of diabetes. She was on anti-hypertensive agents and thyroxine replacement. After admission, she was found to have multiple hypoglycemic attacks. Blood tests during her inpatient hypoglycemic attack showed random glucose 2.1 mmol/L, insulin 122 mIU/L (5-10 mIU/L) and C-peptide 3.49 nmol/L (0.27 - 1.27 nmol/L). The results were compatible with endogenous hyperinsulinemia. Diazoxide 50 mg daily per oral was prescribed, with control of hypoglycemic episodes. Contrast computer tomography (CT) of the abdomen revealed a 1.2 cm enhancing pancreatic head nodule (Figure 1). The main differential diagnoses included pancreatic neuroendocrine tumor and hypervascular metastasis from known thyroid cancer. Arterial stimulation with venous sampling (ASVS) was performed: 10% calcium gluconate was injected at common hepatic, gastroduodenal, superior mesenteric and splenic arteries sequentially, and blood was sampled from bilateral hepatic veins after each injection. Serum insulin was elevated when calcium was injected in GDA and thus the pancreatic head lesion was likely insulinoma. Endoscopic ultrasound (EUS) was performed confirming the 1.2 cm × 1 cm circumscribed heterogeneous mass over pancreatic head, with close proximity to common bile duct (CBD) and main pancreatic duct (MPD) although tissue planes were preserved (Figure 2). Both CBD and MPD were not dilated. EUS-guided fine needle aspiration cytology (FNAC) was performed. FNAC result later confirmed well-differentiated neuroendocrine tumour. In view of patient's age and underlying metastatic thyroid malignancy, pancreatic head insulinoma enucleation with possibility of pancreatodudenectomy (Whipple operation) due to close proximity to CBD and MPD was deemed high risk for her. EUS-guided ethanol injection was offered. During the procedure, 1.5 ml 95% ethanol was injected into the lesion under EUS guidance. The procedure was uneventful and well tolerated. Soon after EUS with ethanol injection, diazoxide was stopped and there were no more hypoglycemic episodes. Blood glucose monitoring remained from 5 to 7. She was discharged on day 4. CT scan 4 months after the procedure showed that the previously seen pancreatic head tumour had resolved, with residual hypoenhancement (Figure 3). The patient was latest seen 1 year after ethanol injection and she remains asymptomatic and no hypoglycemic attacks were noted.

Discussion

Insulinoma is one of the most common types of neuroendocrine tumors with hormonal manifestion. And it is the most common cause of endogenous hyperinsulinemia [1]. More than 95% of insulin is benign [1,2]. Long-term cure with resolution of symptoms are expected after complete resection. Cytoreduction with maximal resection of tumor is also indicated for symptom

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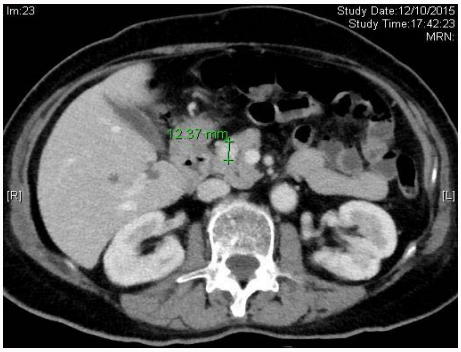

Figure 1: Contrast CT abdomen showing enhancing lesion over pancreatic head before ethanol injection.

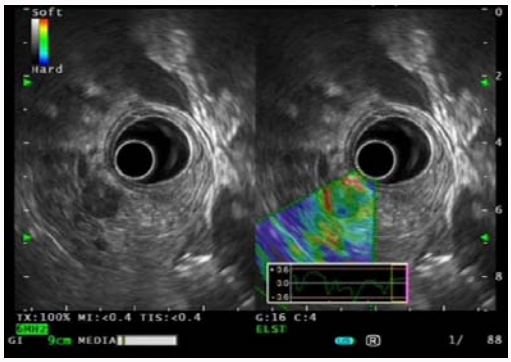

Figure 2: Pancreatic insulinoma detected under EUS (arrow).

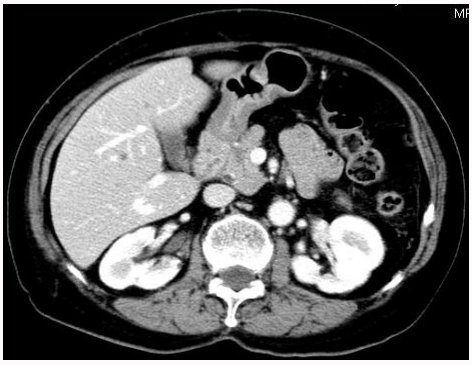

Figure 3: Contrast CT abdomen showing the previously enhancing lesion in pancreatic head became hypodense after ethanol injection.

and hormonal control in patient with metastasis [2] because of low possibility that malignant insulinoma, enucleation without margin or regional lymph node dissecteion is feasible to achieve cure. However if tumor is large, presence of multiple lesions, or close to/involving pancreatic duct, major resection, i.e. pancreatectomy will be required. While the extent of pancreatectomy depends on location of tumor, major pancreatectomy namely Whipple operation, pylorus-preserving pancreaticoduodenectomy, subtotal pancreatectomy or distal pancreatectomy carry high morbidity even in high volume centers being 10% to 43%, respectively [3]. Contemplating a high morbitidy operation to cure a benign disease is less than satfiactory. The situation worsens if this operation were undergone in a patient with medical comorbidity or advance age. A less invasive ablative procedure could be beneficial.

EUS is one of the most sensitive localization methods for pancreatic insulinoma, up to 75%, though sensitivity is operator-dependent [4]. By localizing the insulinoma, EUS-guided ethanol injection to pancreatic tumor for ablation can be contemplated. It is a new minimally invasive therapeutic procedure for small neuroendocrine tumors with accumulating evidence from the literature [5-19] (Table 1). Up till now, 30 patients have undergone EUS-guided ethanol ablation for pancreatic insulinoma. Majority of the procedure (14/18) was performed for pancreatic head lesions. While surgical resection of pancreatic head lesion lead to high risk of complication, EUS guided minimal invasive interventation offer an option for treatment for insulinoma. It reflected by the fact that high proportion of procedures was undergone for pancreatic head lesion. On the

Table 1: Summary of case reports/series about EUS-guided ethanol injection for pancreatic insulinoma.

Author	Year	Patient no, age/sex	Tumor size (largest diameter)	Tumor location	Adverse events	Ethanol injection (average)
Jürgensen [10]	2006	1, 78/F	NA	NA	Nil	8.0mL of 95%
Deprez [6]	2008	1, 78/F	NA	Head	Pancreatitis, haematoma, duodenal ulcer	3.5ml of 98%
Muscatiello [8]	2008	1	7-11mm	NA	Pancreatic necrosis requiring laparoscopic necrosectomy	2ml
Vleggaar [11]	2011	1, 82/F	9.5 mm	Body	Nil	0.3 ml of 96%
Levy [9]	2012	8, 34-82 years old (3 patients had intra-operative US)	15mm	Head: 6 Body: 1 Tail: 1	Nil	0.8ml
Schnack [7]	2012	1, 89/M	NA	NA	Pancreatitis	NA
Lee [12]	2013	NA	NA	NA	NA	NA
Bor [13]	2014	1, 83/F	NA	Head	Nil	3ml
Qin [14]	2014	4, 48-66 years old	5-11mm	Head: 3 Body: 1	Nil	0.25-0.5ml of 95%
Yang [15]	2015	4, 47-68 years old	NA	NA	Nil	3.1ml of 98%
Paik [5]	2016	3 insulinoma 5 other NET	9-14mm	Head	2 abdomen pain 1 self-limiting fever 1 pancreatitis	1.2–10.5 mL
Trikudanathan [16]	2016	1, 66/M	14mm	Head	Nil	1ml
de Sousa Lages [17]	2017	1, 89/F	12mm	Body	Nil	0.6 mL of 95%
Mittal [18]	2017	NA	NA	NA	NA	NA
Luo [19]	2017	1, 32/M	NA	Head	Nil	NA

other hand, EUS-guided ethanol ablation was mainly performed in elderly or poor surgical candidates due to comorbidities, patients who refused operation but refractory to medical treatment, and persistent lesions after resection or multiple lesions especially associated with MEN 1. The response of ethanol ablative treatment was determined by resolution of recurrent hypoglycemic symptoms. Most of the studies reported no or minimal adverse effects after procedure. Mild adverse events included transient abdominal pain and self-limiting fever. More severe complications, including pancreatitis, pancreas necrosis or duodenal ulcer have been reported. At the moment, there are no definite selection criteria for pancreatic insulinoma amenable by EUS ethanol injection. All lesions in the reported cases are less than 2 cm in size, and have to be localized and being accessible by EUS. On the other hand, there were no guidelines suggesting the dosage of alcohol or type of injection needle. Occasionally, repeated injections of ethanol in different sessions are required. In our patient, 22-gauge needle with 1.5 ml absolute ethanol was only injected once. Some advocates that injecting a smaller volume of ethanol than estimated for the tumor volume could prevent procedure-related adverse events, such as leakage of ethanol and post-procedural pancreatitis. In addition to procedure-related complications, the major concern of local ablation therapy is oncological clearance, i.e. failure in complete ablation or recurrence. In the literature there are no long-term data regarding recurrence for pancreatic insulinoma or other neuro-endocrine tumor treated with EUS ethanol injection. For insulinoma, disease response and recurrence could be monitored by presence of symptoms and imaging which may show hyper-enhancing features of the ablated lesion. For persistent or recurrence of NET without signs of distant metastasis, repeated complementary ethanol ablation therapy could be applied. Surgical resection should be considered if repeated ethanol ablation failed to cure the condition. However, most of these patients who optioned for EUS ethanol ablation were too fragile for major operation and thus conservative treatment and monitoring were usually offered.

Conclusion

In conclusion, EUS-guided ethanol ablation for insulinoma is a promising options but not yet a standard alternative to surgical resection, with lack of long-term results and technical standardization. However, it is a useful alternative for patients who have small tumor, and are not fit for operation. We postulated that even in insulinoma with metastatic disease, EUS-guided ethanol could be considered for symptoms and hormonal control. For persistent or recurrent disease, repeated sessions of ethanol injection is possible. Although procedure-related adverse events are not common and usually mild, severe complications such as pancreatitis or necrosis could occur and thus careful injection technique and close monitoring after procedure are advocated.

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