Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma

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Abstract

Objective : **Most insulinomas are benign sporadic tumours that require complete resection to avoid recurrent symptoms of hypoglycaemia. Alternate minimally invasive therapies are seeked in elderly patients in whom extensive surgery might be life-threatening. We wanted to evaluate the feasibility, safety and efficacy of ethanol injection using endoscopic ultrasound (EUS) guidance to ablate a pancreatic insulinoma.**

Patient and methods : **A 78-yr-old female patient was referred in our academic medical centre for symptomatic hypoglycaemia. Laboratory and imaging work-up confirmed the diagnosis of an insulinoma presenting as a small tumour located deeply in the pancreas head, in close vicinity with the Wirsung's duct. Major pancreatic resection was contra-indicated due to the poor condition of the patient. Endosonography using a linear-array endoscope allowed injection of 3.5 ml of 98% ethanol in the pancreatic tumour after endoprosthetic stenting of the biliary and pancreatic ducts.**

Results : **There was no recurrence of hypoglycemia, and fasting tests performed 12 days and 3 months after the procedure showed complete remission of endogenous hyperinsulinism. Complications included a mild and asymptomatic elevation of pancreatic enzymes for 2 days and the later occurrence of medically-controlled hematoma and ulceration of the duodenal wall. Complete normalization of pancreatic head morphology was confirmed by imaging at 3 months and the patient remains currently asymptomatic and normoglycemic more than two years after the procedure.**

Conclusions : **EUS-guided ethanol ablation of sporadic insulinoma is a new feasible and efficient therapy to be considered for small and localized lesions in poor surgical candidates.** (Acta gastroenterol. belg., **2008**, 71, **333-337**).

Key words : insulin-secreting, neuroendocrine tumor, ethanol injection, echoendoscopy.

Introduction

Insulinoma is a rare tumour, with a reported incidence of four cases per 1 million patient-year (1). The majority of these tumours are sporadic and benign, measure less than 2 cm in diameter, and require complete surgical excision to avoid recurrent symptoms of hypoglycaemia (2). Depending on their size and location, insulinomas can be enucleated or might require more extensive surgery, such as a distal pancreatectomy or Whipple's cephalic pancreatico-duodenectomy (3). The mortality rate after pancreatic surgery has significantly decreased in experienced centres (4-6), but the postoperative morbidity remains high, still reaching 30% after laparoscopic resection (6,7) and up to 40-50% after pancreatico-duodenectomy (5,8).

Percutaneous ethanol injection has become a commonly used therapeutic modality for several types of solid or cystic tumours, such as small hepatocellular carcinomas (9,10) or thyroid nodules (11), offering benefits often equivalent to surgery with low cost and morbidity. In the pancreas, ethanol injection has been used so far only in a few selected cases, to treat non resectable cancers by the percutaneous route (12) or pancreatic cysts via endoscopic ultrasound (EUS)-guidance (13). Very recently, one case of alcohol injection into a small insulin-producing pancreatic tumour has been reported with symptomatic remission but persistence of a moderate hyperinsulinism (14).

We report here a well-documented case of EUS-guided ethanol ablation of an insulinoma and show that this technique was feasible, efficient, and had an acceptable morbidity in a patient who was a poor candidate for pancreatic surgery. We also discuss the potential advantages and limitations of this technique in the case of benign pancreatic neuro-endocrine tumours.

Case report

A 78-year-old Portuguese woman was admitted in the emergency room for an episode of severe dizziness with diaphoresis, blurred vision, confusion, and transient loss of consciousness, suddenly occurring while she was visiting her family in Belgium. Her serum glucose level was low at 35 mg/dl (1.9 mmol/liter), and the symptoms completely resolved after a 20 ml-iv injection of 30% glucose. The patient reported that she had experienced similar though less severe symptoms since several months. She also complained of exertional dyspnea and chest pain. Medical history included hypertension and a severe aortic stenosis diagnosed 2 years before, for which she had refused surgery. She was routinely treated with small doses of spironolactone, acetylsalicylic acid, and aclofenac, a non-steroidal anti-inflammatory agent. There was no remarkable family history. On physical examination, the patient had a high BMI (29.0 Kg/m^2), mildly elevated blood pressure (160/90 mm Hg), and an

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Table 1. — **Laboratory findings during hypoglycaemic episodes**

	Day 1* 07:30	Day 1* 19:00	Day 2* 05:40	Day 2* 23:45
Glucose [mg/dl (mmol/liter)]	45 (2.5)	35 (1.9)	37 (2.1)	31 (1.7)
Insulin (pmol/liter)	150.7	229.6	114.8	193.7
C peptide (nmol/liter)	ND	ND	1.97	ND
Urinary sulfonylurea	Negative (a)		Negative (b)	

* : values obtained at the times indicated during spontaneous hypoglycaemic episodes occurring on days 1 and 2 after admission of the patient.
(a) : on urinary spot taken after hypoglycemia ; (b) : on 24-h urine collection.
ND : not determined.
The diagnosis of insulinoma was based on treshold levels recommended by Service (reference 15) : glucose ˝ 45 mg/dl (2.5 mmol/liter), with insulin (by immunoradiometric assay) > 36 pmol/liter, C peptide ≥ 200 pmol/liter, and no evidence of sulfonylurea intake.

intense systolic murmur of aortic origin. Abdominal examination was normal. The patient was hospitalized for further investigations.

Recurrent hypoglycaemia was demonstrated, concomitant with high insulin and C peptide concentrations, leading to the diagnosis of insulinoma (Table 1). The search for sulfonylurea intake was two-fold negative. Adrenal and pituitary insufficiencies were ruled out (cortisol at 679 nmol/liter at the time of hypoglycaemia), as well as multiple endocrine neoplasia type 1 (MEN1) syndrome. The subsequent work-up was made under continuous iv 10% glucose infusion.

A computed tomogram (CT) of the abdomen was performed (Fig. 1A) and showed a well-delineated 14 × 16 × 20 mm mass, located in the head of the pancreas, markedly enhancing after contrast injection (from 45 to 168 Hounsfield units at arterial time). There was no other abnormality, except for multiple gallstones. Endoscopic ultrasonography confirmed the presence of a heterogeneous pancreatic nodule of 17 mm-diameter (Fig. 2A), located nearby the cephalic part of the Wirsung duct, with peripheral hypervascularization. There was no associated lymphadenopathy. A somatostatin-receptor scintigraphy (111-indium pentetreotide – Octreoscan) showed no pathological uptake, especially in the pancreatic and liver regions.

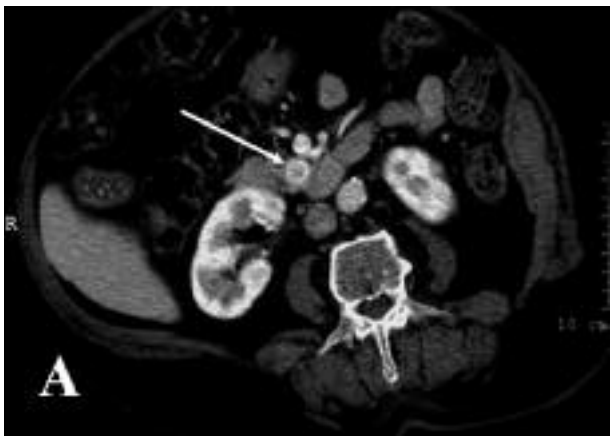
A critical aortic stenosis (effective valve area = 0.80 cm^2 ; mean aortic gradient = 50 mm Hg) and a long stenosis (> 60%) of the anterior descending coronary artery were diagnosed by arteriography during the presurgical evaluation of the patient, precluding immediate pancreatic surgery. Aortic valve replacement and myocardial revascularization with the left internal mammary artery were performed under extracorporeal circulation. The post-operative course was complicated by recurrent hypoglycaemia and a severe bronchopulmonary infection with acute respiratory failure.

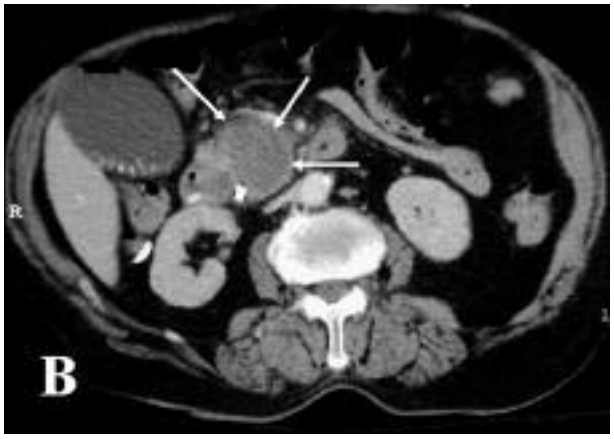
The precarious health status of the patient, together with the likelihood that peroperatively a major pancreatic resection would be necessary (because of the deep intraparenchymal location of the tumour and its close contact with the Wirsung duct), led us to consider endoscopic ultrasound (EUS)-guided ethanol injection of the tumour as a potential alternate treatment of this apparently sporadic and benign insulinoma. After giving informed consent, the patient underwent a new endoscopic procedure combining endoprosthetic stenting of the biliary and pancreatic ducts, performed to prevent subsequent ductular stenosis and endosonography, using a linear-array endoscope (EG3830 UT, Pentax Hamburg, Germany) and a Hitachi EUS-8500 processor (Heverlee, Belgium). The pancreatic tumour was then injected, with a total of 3,5 ml of 98% ethanol under EUS guidance, using 21-25 gauge needles (EUSN, Cook Ireland Ltd, Limerick, Ireland), until the hypoechogenic tumoral mass was no longer distinguishable from the surrounding pancreas (Fig. 2B). A small amount of ethanol was seen flowing back through the duodenal wall puncture tract.

After this procedure, the patient was treated with antibiotics for 7 days and proton-pump-inhibitors (omeprazole 40 mg/day) to prevent duodenal ulceration. She remained asymptomatic until day 14. Laboratory testing showed after one day a mild elevation of amylase (peak 79 U/liter ; normal values : 12-66 U/liter) and lipase levels (109 U/liter ; normal values : 2-62 U/liter), which fully normalize after 48 hours. A control abdominal CT was performed on day 7 and disclosed a well-delimited necrotic area of 27 × 28 mm at the site of the pancreatic mass, with a markedly decreased contrast enhancement (not shown).

Two weeks later, the patient developed melaena and endoscopy revealed the presence of a ulcer of the duodenal wall, classified as Forrest 2a. CT showed a 50 mm-large haematoma of the wall of the second portion of the duodenum (Fig. 1B). Medical treatment was reinforced (omeprazole 80 mg/day) and the symptoms completely resolved within 48 hours. This was confirmed by progressive reduction of the duodenal hematoma at CT (30 mm at day 18 ; 14 mm at day 25), and disappearance of the ulcer necrosis at control duodenal endoscopy performed after one month.

The evolution of glucose and insulin levels was remarkable. The patient had no recurrence of hypoglycaemia despite progressive withdrawal of the glucose infusion. Short fasting tests were performed after 12 days and after 3 months (Table 2). They showed slightly elevated glucose concentrations and normal insulin and C peptide levels, with no evidence of endogenous hyperin-





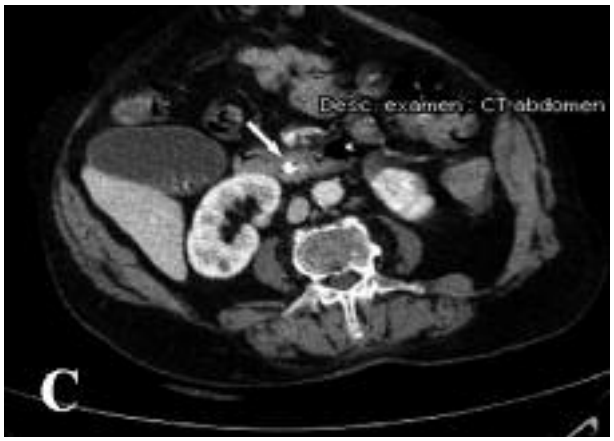


Fig. 1. — Computed tomographic (CT) scan of the pancreas showing : (A) at diagnosis, a well-delineated, contrast-enhanced tumor measuring $14 \times 16 \times 20$ mm, located in the head of the pancreas (white long arrow) ; (B) at day 14 after ethanol injection, the appearance of a 50 mm-large hematoma of the duodenal wall (indicated by the white arrows) ; and (C) 3 months after ethanol injection, a normalized appearance of the pancreas head, except for the presence of endoprosthetic stent in the Wirsung's duct (white short arrow).

sulinism (Table 2). The biliary and pancreatic stents were removed after 2 months without complication. At the same time, the biliary, Wirsung's and Santorini's ducts were opacified and showed a normal morphology, with no sign of stricture. Abdominal CT confirmed the complete normalization of pancreatic head morphology (Fig. 1C). The patient remains today asymptomatic and euglycaemic more than two years after the procedure.

Discussion

We report here a case of successful ethanol ablation of a sporadic insulinoma in an elderly patient who was a poor candidate for extensive pancreatic surgery. Although not formally confirmed by histopathological examination, the diagnosis of insulinoma was undoubtful. The patient exhibited typical features of an insulin-producing tumour, such as the post-absorptive and repeated occurrence of the Whipple's triad : neurologic symptoms of hypoglycaemia, a concomitant plasma glucose level of 2,5 mmol/liter or less, and relief of these symptoms after glucose administration. Furthermore, biochemical criteria allowing to establish the diagnosis of endogenous hyperinsulinism were fulfilled : on several occasions, insulin concentration was markedly elevated above the currently admitted threshold of 36 pmol/liter, and C peptide level was also high (above 200 pmol/liter) when serum glucose was below 45 mg/dl (2,5 mmol/liter) (15). In addition, urinary screening for sulfonylurea was negative. The biological diagnosis of insulinoma was confirmed by imaging, both CT scan and echoendoscopy showing a typical hypoechogenic and highly vascularised tumour located deeply in the pancreas head, nearby the Wirsung's duct and likely non resectable by a simple enucleation.

As it is the case in 90% of the cases (1,2), this insulinoma appeared to be a sporadic and benign tumour, being solitary, confined to the pancreas, of regular shape and small size (less than 2 cm in diameter), without evidence of adenopathy or liver metastasis. It also occurred in an old patient, without familial history of endocrinopathy or sign of MEN1. All these features have also contributed to the therapeutic choice of ethanol tumour ablation as a reasonable alternative to surgical resection in our patient.

The standard treatment of insulinoma remains its surgical resection by enucleation, or through a more extensive pancreatic resection in cases of multiple, extensive or invasive tumours, or when the neuro-endocrine tumour is close to the pancreatic or biliary ducts (3,6). While postoperative mortality has improved over the last two decades, morbidity continues to be high (30-50%), independent of the surgical technique used (4-8). Pancreatic leakage remains a frequent complication, occurring in 5-30% of the cases, while abdominal bleeding, abscess or wound infections may also be observed. Alternative therapy may include medical treatment with diazoxide (16) or with a somatostatin analogue, as reported in a few cases (17), but these drugs are not curative, have known side-effects, and allow long term control only in a minority of insulinomas (18). In addition, a somatostatin-receptor scintigraphy performed in our

Table 2. — **Short fasting tests performed on days 12 and 90 after ethanol ablation of insulinoma**

	Day 12*			Day 90*	
Duration of fast	12-h-fast	18-h-fast	24-h-fast	12-h-fast	24-h-fast
Glucose [mg/dl (mmol/liter)]	111 (6.2)	108 (6.0)	103 (5.7)	108 (6.0)	108 (6.0)
Insulin (pmol/liter)**	57.4	43.1	43.1	57.4	35.9

* : Day after ethanol injection of the pancreatic tumor.
** : conversion factor : 1 µU/ml = 6 pmol/liter ; normal values < 60 pmol/liter.

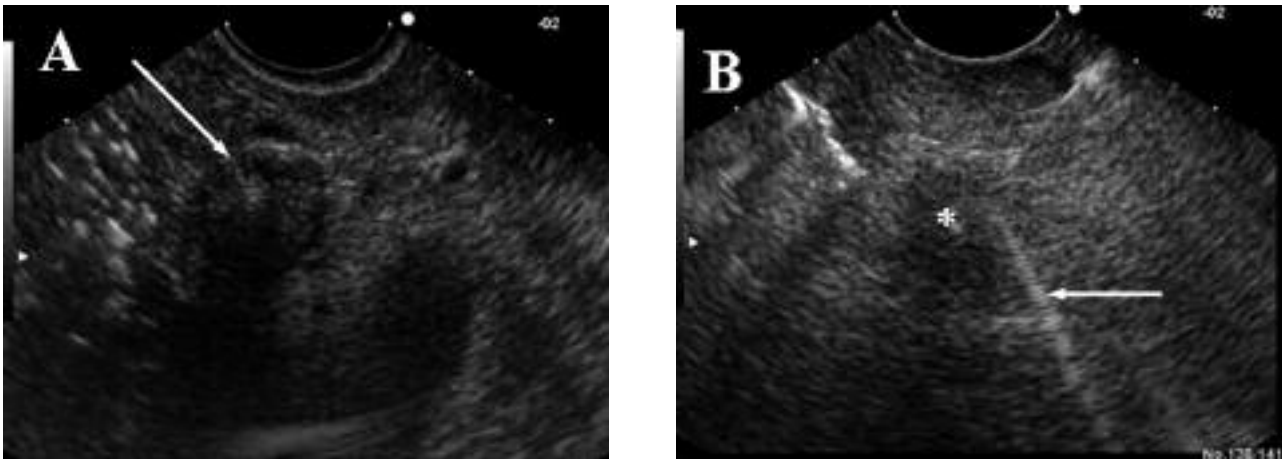


Fig. 2. — Endoscopic ultrasound of the pancreas confirming (A) at diagnosis, the presence of a typical, round and hypoechogenic neuroendocrine tumor in the head of the pancreas (white arrow) ; and (B) the position of the 25 gauge needle (white arrow) during ethanol injection of the pancreatic tumor, which caused a progressive disappearance of the hypoechogenic mass corresponding to the insulinoma (localized by a white star).

patient was negative, indicating a low amount of somatostatin receptors in the insulinoma, as it is often the case in this type of neuroendocrine tumour (19).

Therefore, in some selected cases, non surgical targeted ablation of an insulin-producing pancreatic tumour with ethanol or radiofrequency might become in the future a minimally invasive first-line option. The feasibility and safety of both EUS-guided radiofrequency application (RFA) and alcohol injection in the pancreas have been already demonstrated in a porcine model (20,21). However, though well described by the laparoscopic or percutaneous approaches (22,23), RFA ablation of pancreatic neuroendocrine tumours via EUS guidance remains currently hampered by the unavailability of endoscopic radiofrequency probes specifically designed for human applications. In contrast, the EUS-guided ethanol injection technique is readily accessible to experienced endoscopists.

Until recently, EUS has been mostly used in clinical practice for the diagnosis and staging of pancreatic and upper gastrointestinal tract tumours (24). EUS is the most sensitive preoperative imaging technique to localize insulinomas, with an accuracy rate reaching 80-90% (25). EUS-guided fine-needle aspiration (FNA) is also a safe and convenient technique for the cytopathological diagnosis of pancreatic neuroendocrine tumours (26). The same needles used for FNA can also be used to inject substances, such as alcohol, corticosteroids or anaesthetic agents, for example to achieve celiac plexus blockade (27). In a few selected cases, EUS-guided injection of alcohol has been performed in attempts to ablate tumours such as liver metastases (28) or gastrointestinal stromal tumours (29). Ethanol (5-80%) lavage of pancreatic cyst lesions has also been performed safely and successfully through this route (13). In one recent case, injection of alcohol into an insulinoma was also briefly reported, without major complication and with a durable symptomatic remission, though some degree of hyperinsulinism persisted 20 months after the procedure (14).

Such EUS-guided ethanol treatment of a pancreatic neuro-endocrine tumour offers numerous potential advantages, such as its easiness and rapidity when performed by an experienced endoscopist, its low cost, and an acceptable morbidity even in patients with poor general conditions. Several limitations of the technique need, however, to be pointed out. Only patients with small (less than 20 mm-diameter), well-demarcated, and round tumours that are likely benign and accessible through endoscopy will be good candidates for this treatment. In the specific case of insulinoma, giant, multiple or malignant tumours represent relative contra-indications, as symptoms of hypoglycaemia will likely persist or recur after targeted ablation.

The risks of this new technique are not fully established yet. EUS-guided FNA has proven to be a safe

method, with a very minimal rate of bleeding, pancreatitis or infection, although the needle must traverse the gastrointestinal wall to enter sterile spaces and large vascular structures are in close vicinity (24,26,27,30). Modern linear array EUS with colour Doppler enables the selection of an injection path devoid of vascular structures, and antibiotic prophylaxis minimizes the risk of nosocomial infection. A rare but recognized complication of percutaneous ethanol injection into hepatic malignant tumours is the implantation of tumour cells along the needle tract (31). This risk should be minimized in the setting of pancreatic neuro-endocrine tumours if malignant tumours are not selected for the procedure, and if a short distance of needle insertion is used as it is the case with EUS-guided procedures.

In our case, immediate local complications included a mild and asymptomatic elevation of pancreatic enzymes during the two first days, and the late occurrence of a secondary ulceration and haematoma of the duodenal wall, due to the backflow of ethanol after injection. Although potentially severe, this complication subsided rapidly under conservative medical treatment, and was not associated with concomitant acute pancreatitis. We could also demonstrate full restoration of normal duodenal and pancreatic morphology after three months. Such a risk of secondary duodenal or pancreatic necrosis will require a careful monitoring of the patient in a hospital setting, but might be minimized in the future by using lower (30-80%) ethanol concentrations, as recently suggested by Aslanian and colleagues in a porcine model (21) or by Gan *et al.* in a pilot study evaluating the safety of ethanol lavage of pancreatic cysts (13). In addition to the concentration used, the total volume of ethanol injected might also play a critical role and we suggest to inject smaller amounts (1-2 ml) of ethanol with a small calibre needle (25 gauge).

In summary, this case report shows that EUS-guided ethanol ablation of a symptomatic insulin-producing pancreatic tumour is a feasible and efficient procedure, with an acceptable morbidity. This new technique might therefore be considered as a first-line therapeutic option for localized lesions in poor surgical candidates. These preliminary but encouraging results need to be confirmed at longer term and in larger series of patients.

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