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CASE REPORT

Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review

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Abstract

Here we offer a review of the literature regarding endoscopic ultrasound-guided ethanol ablation for pancreatic neuroendocrine tumours and describe the case of a cystic tumour completely ablated after a multisession procedure. A total of 35 PubMed indexed cases of treated functioning and non-functioning pancreatic neuroendocrine tumours resulted from our search, 29 of which are well-documented and summarised. Endoscopic ultrasound-guided ethanol ablation appears as a local, minimally invasive treatment of pancreatic neuroendocrine tumours, suitable for selected patients. This technique appears feasible, relatively safe and efficient, especially when applied to symptom relief in functioning tumours, aiming at loss of endocrine secretion. For non-functioning tumours, where the goal is complete tissue ablation, eus guided ethanol ablation can provide good results for patients who are unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients requires assessment through further studies.

Key words: Endoscopic ultrasound; Pancreatic neuroendocrine tumour; Endoscopic ultrasound-guided injection; Ethanol; Tumour ablation

Core tip: We report a complete review of the literature about endoscopic ultrasound-guided ethanol ablation for pancreatic neuroendocrine tumours. The case of a cystic tumour completely ablated after a multisession procedure is described. On long term follow-up a durable

remission of the tumour was obtained; a complete image gallery showing the pre and post-treatment appearance is available. The technical aspects, clinical success and complication rates related to this kind of procedures are described.

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INTRODUCTION

In recent years the improvement of diagnostic and therapeutic technologies has led to less invasive treatments in any field of medicine with a shift from surgery to imaging guided treatments.

Endoscopic ultrasonography (EUS) has demonstrated excellent diagnostic accuracy for bilio-pancreatic district diseases and high safety and precision when applied for operative purposes. Along the years this peculiarity has made of EUS an optimal technique for imaging and cytological diagnosis, as well as for execution of more advanced procedures (*i.e.*, drainages and local treatments).

The current management of T1 and T2 pancreatic neuroendocrine tumours (pNETs) is somewhat similar to that of most pancreatic tumours (surgical resection), with a considerable economic burden and post-operative complications. However we are dealing with a pathology that offers a better prognosis and that is potentially responsive to local treatments[1,2].

Neuroendocrine tumours arise from cells present in the diffuse endocrine system and can be found throughout the body. They are most commonly located in the gastrointestinal tract and lung but are also found in the pancreas[3]. The 2010 World Health Organization (WHO) classification divides the pNETs in three grades (G1, G2 and G3) on the basis of Ki-67 nuclear antigen expression (< 2%; 2%-20% and > 20%) and mitotic rate (< 2; 2-20 and > 20). Biopsy is most commonly used to assess the grade of the tumour. According to the TNM, the tumour is classified as T1a (< 1 cm), T1b (1-2 cm) and T2 (larger than 2 cm); T3 and T4 are locally advanced tumours (Table 1).

Tumour grading and tumour stage are the main prognostic factors of pNETs. Well and moderately differentiated have a significantly better survival compared to poorly differentiated neuroendocrine carcinomas.

pNETs are also classified as functioning and non-functioning depending on the secretion of specific hormones. Functioning tumours are commonly associated with a specific hormonal syndrome directly related to a hormone secreted by the neoplasm such as insulinomas with ipoglicemia, gastrinomas with Zollinger–Ellison or carcinoid syndrome. Most non-functioning tumours occur in the head of the pancreas and produce mass effect symptoms. When small, they are usually incidentally discovered due to the incremental use of high-level diagnostic imaging.

Table 1 World Health Organization classification of pancreatic neuroendocrine tumors

Grade	Ki-67 index (%)	Mitotic count/10 HPF
G1	≤ 2	< 2
G2	3-20	2-20
G3	> 20	> 20
TNM	Size (cm)	Muscularis propria invasion
T1a	< 1	–
T1b	1-2	–
T2	> 2	+

Accordingly to the WHO classification 2010, the higher grade is assumed if the Ki-67 index and mitotic count differ; in the WHO 2010 TNM, the tumor is classified as T2 if it is larger than 2 cm in diameter or if it invades the muscularis propria. T3 and T4 tumors are locally aggressive tumors. WHO: World Health Organization; HPF: High-power field.

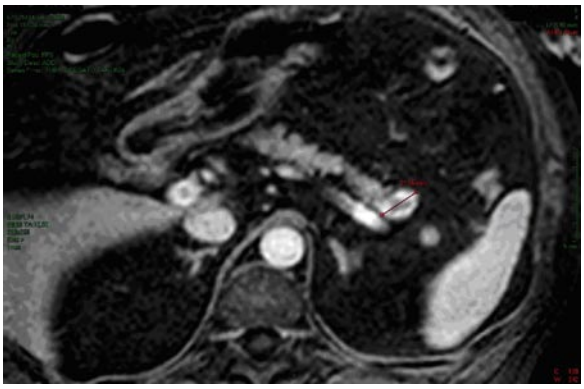

Figure 1 Abdominal magnetic resonance imaging demonstrating a round, well-demarcated nodule of the pancreatic tail. The 22 mm lesion (calipers) shows highly vascularised peripheral tissue.

EUS is the optimal diagnostic modality and can provide a biopsy specimen for histological confirmation and differentiation grade. The EUS image is usually of a solid, ipoechoic, round and smooth nodule, sometimes with a cystic central component (bull's eye appearance).

To date, the management of pancreatic sporadic, small (< 2 cm), asymptomatic, low-grade (G1) NETs suggests a "wait and see" strategy. Surgical resection of non-functioning pNETs is actually recommended for large (> 2 cm) or G2-G3 lesions[4]. For patients unfit for surgery due to high-risk comorbidity or for those who refuse resection, the EUS-guided ethanol ablation has been reported in a few cases[5] as a local and minimally invasive therapy.

CASE REPORT

A 58-year-old man with essential hypertension and recent onset of glucose intolerance was referred for a

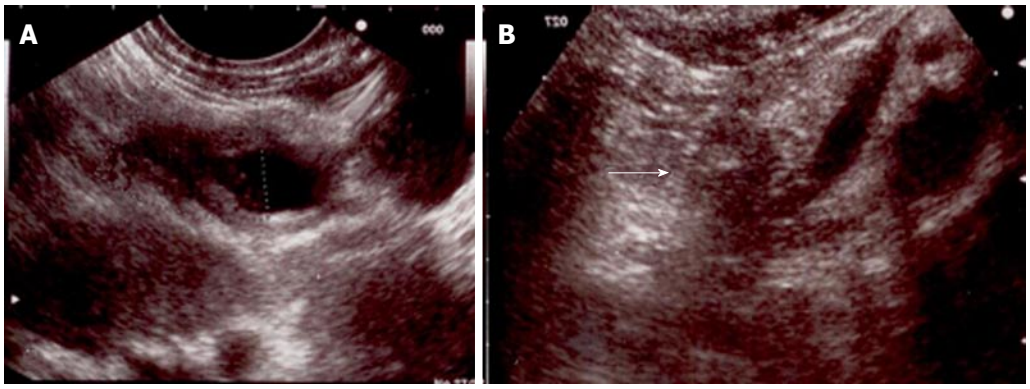

Figure 2 Endoscopic ultrasound appearances before (A) and after (B) treatment (white arrow).

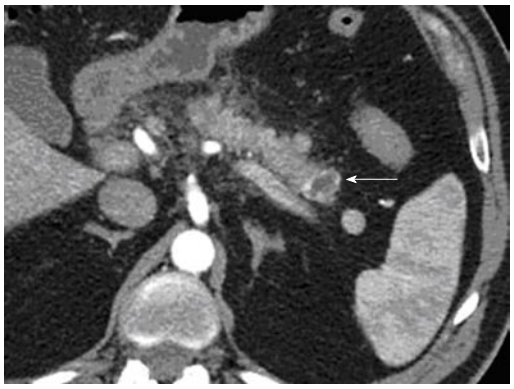

Figure 3 Computed tomography scan showing thin residual hypervascular tissue (white arrow) two months after the first treatment.

transabdominal ultrasonography (US). Other laboratory test results including levels of carcinoembryonic antigen and carbohydrate antigen were all within normal ranges. The US session diagnosed a focal lesion on the pancreatic tail. An abdominal magnetic resonance image showed a 22 mm nodule with peripheral hypervascularization (Figure 1), and EUS confirmed a "bull's-eye" appearance nodule with peripheral hypervascular pattern *via* power Doppler and a central cystic component. The EUS-guided FNA of the lesion confirmed the diagnosis of pNET. The Ki67 proliferative index was > 5% to yield a G2 grade. However, because the patient adamantly refused surgical resection, we decided to ablate the lesion *via* EUS-guided ethanol injection.

After aspiration of the cystic component, a mean volume of 1.7 mL of 95% ethanol per session was injected into the tumour and re-aspirated using a 25-gauge needle (Echo-tip ultra, Cook, Limerick, Ireland) through a linear array echoendoscope (Figure 2). Three treatment sessions over six months were performed to ablate the nodule (Figure 3).

The hospitalization time was 2 d for each session. The patient experienced mild pancreatitis in 2 out of 3 sessions - that resolved with standard-of-care. No major or late complications were observed. After 24 mo, we achieved a durable and complete remission of the tumour as shown by CT and EUS morphological imaging (Figure 4).

DISCUSSION

Most diagnosed pNETs are non-functioning tumours (90.8%); the remaining 9% are malignant functioning tumours such as gastrinomas (4.2%), insulinomas (2.5%), glucagonomas (1.6%), and VIPomas (0.9%). Although commonly perceived to be indolent tumours, they exhibit a broad range of growth rates, malignant potential, and overall prognosis. Most patients with pNETs (60%-70%) present with metastatic disease at diagnosis. Following surgical resection, the 5-year cumulative survival for pNETs other than insulinomas is roughly 65% with a 10-year survival of 45%[6].

Patients with incidental diagnosis of pNETs with a tumour size < 2 cm and low-grade (G1) dysplasia have a 5-year overall survival of 100% with a minimal risk of recurrence[6]. In this setting, a "wait and see" policy is recommended.

On the contrary, surgical resection is the standard treatment for functioning and non-functioning G2-G3 pNETs. However, this is associated with a high risk of complications. Even when performed in high-volume centres, typical pancreatic resections (pancreaticoduodenectomy or distal pancreatectomy) have a mortality rate of about 5% with complications ranging from 40% to 50%[7]. This is particularly common in the elderly or patients with comorbidities. Typical pancreatic resections are also associated with a high incidence of exocrine and endocrine insufficiency.

In an attempt to reduce complications and pancreatic impairment, new parenchyma-sparing resection techniques such as enucleation and middle pancreatectomy (resection of the central part of the gland) have been applied to small tumours[8]. Although pancreatic head tumour enucleation resulted in decreased operative time and length of hospitalization, the 5-year survival and overall morbidity and mortality were comparable to standard surgical resection even for small pNETs[9]. To date, no alternative treatment has been standardized for patients unfit for surgery or for those who refuse

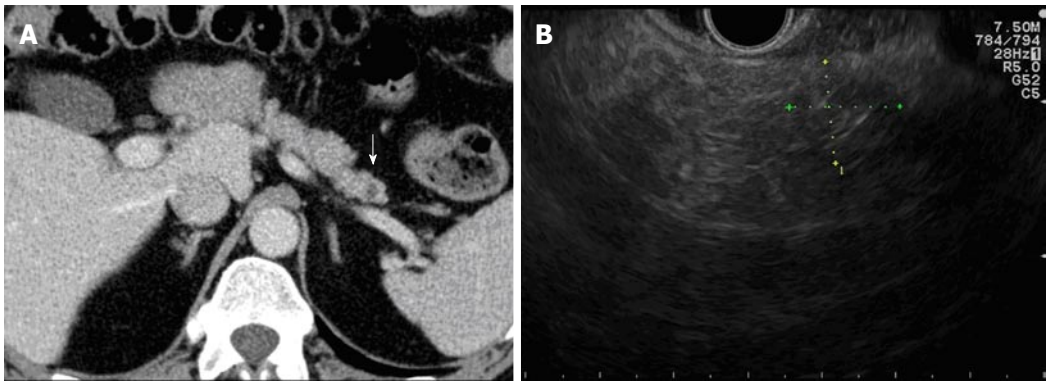

Figure 4 Twenty-four months follow-up. A: Computed tomography scan showing absence of hypervascular tissue around a small hypodense area (white arrow); B: Endoscopic ultrasound scan of the pancreatic tail demonstrating poorly defined hyperechoic tissue (fibrosis) with posterior shadow (caliper).

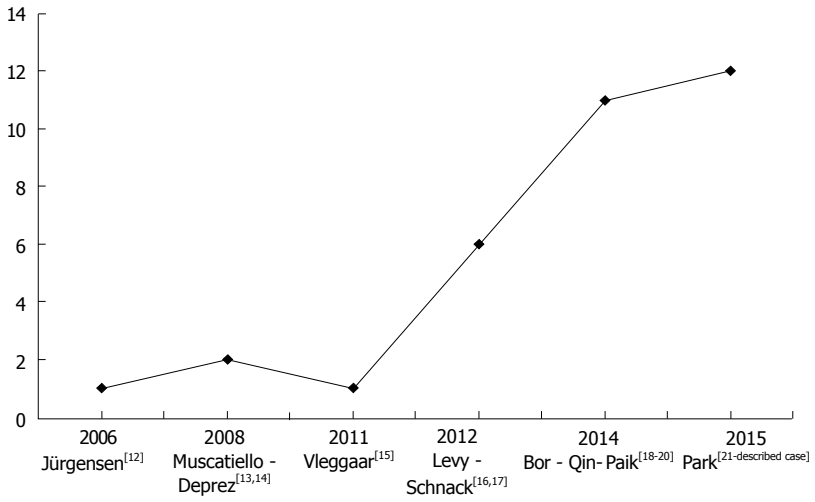

Figure 5 Reported endoscopic ultrasound-guided ethanol ablation procedures over time. Literature review showed a progressive increase of performed procedures from 2006 to 2015. Cases described in abstract form by Paik *et al*[20] were not included in the final results analysis.

resection.

In the recent decades, EUS has evolved into a useful therapeutic tool for treating a broad range of tumours. EUS-guided injection has been applied both as a pancreatic cancer treatment aimed at controlling pain through nerve blockade as well as a solid tumour therapy for the introduction of brachytherapy seeds and viral vectors or as a tool for ablation therapy[10,11]. The pNET EUS-guided ethanol ablation is a new, less invasive therapeutic option although it remains rare.

A PubMed literature review showed 26 patients affected by small pNETs (maximum diameter of 21 mm) who underwent EUS-guided ethanol ablation[12-21] including 19 functioning and 10 non-functioning tumours (Table 2). The number of patients treated by this tecnique progressively increased from 2006 to 2015 (Figure 5).

Conscious sedation is generally reported during the procedure. A mean hospitalization time of 2 d/session is usually necessary even in the absence of complications.

Technical success is reported in 100% of cases; a 22 or 25 gauge needle was generally used to inject a small volume of ethanol with a range between 0.2 and 8 mL per session. The choice of ethanol volume is a function of tumour size. For small ($\leqslant$ 20 mm) tumours, Qin *et al*[19] suggested that the volume be calculated as follows. For round tumours, the volume of ethanol corresponds to half the tumour size; for oval or irregular tumours, the volume of ethanol is (major axis + minor axis of the tumour)/2. A 1.0 mL syringe should be used for precise injection.

In terms of therapeutic outcomes, differentiation of functioning and non-functioning tumours seems to be very important. For small functioning symptomatic G1 tumours, the aim of the ablation is the symptom relief. For non-functioning tumours, the treatment goal is complete ablation of the lesion as confirmed by imaging.

Including the case here described, this technique achieved clinical success (complete symptom resolution) in 100% of 19 functioning tumours with a mean follow-up of 13.6 mo (range 2-38). Ethanol ablation is less effective for non-functioning tumours with a reported success (complete radiological ablation) of 70% (7/10 tumours were ablated, one lost to follow-up) with a mean follow-up of 13.4 mo (range 3-24) (Table 2). The reason is unclear but it might be due to a "debulking" effect in functioning ones, resulting in loss of endocrine

Table 2 Patient demographic information and baseline characteristics of the tumours

No. of patients[1]	27
Age, yr	
Mean (range)	59 (27-89)
Sex, male/female	10-17
No. of tumors	30
Functioning	19
Non functioning	11
Type of functioning tumor	
Insulinoma	18
Vipoma	1
Diameter, mm	
Mean (range)	12.5 (5-22)

[1]Including described case.

Table 3 Procedural outcomes

No. of treatment session per tumor	
Mean (range)	1.43 (1-3)
Alcohol volume, mL	
Mean (range)	1.83 (0.18-8)
Technical success, *n* (%)	30/30 (100)
Clinical success[1], *n* (%)	
Functioning	19/19 (100)
Non functioning[2]	7/10 (70)
Adverse events[3], *n* (%)	11 (25.5)
Early (within one week), *n* (%)	9 (21)
Pancreatic necrotic lesion	1 (2.3)
Mild pancreatitis	7 (16.2)
Abdominal pain	1 (2.3)
Late, *n* (%)	2 (4.6)
Hematoma and ulceration of the duodenal wall	1 (2.3)
Main pancreatic duct stricture	1 (2.3)
Follow-up, mo	
Mean (range)	13.4 (2-38)

[1]Clinical success: Symptom resolution for functioning tumours and radiological ablation for non-functioning tumour; [2]One non functioning tumor was lost to follow-up; [3]Adverse events percentage is intended in relation to procedure number.

secretion, although with persistent viable tissue, or to a more aggressive histological grading of non-functioning tumours. Unfortunately, lesion grading was not available in most of the reviewed cases.

Few early complications (within one week) are reported: 7 mild pancreatitis cases were observed (16.2%) out of 43 procedures. One (2.3%) major early complication was described[13]: A pancreatic necrotic lesion that was likely caused by ethanol effusion. It was managed by laparoscopic necrosectomy.

Two (4.6%) late complications occurred: One hematoma and ulceration of the duodenal wall[14] and main pancreatic duct stricture[21]. These were managed by endoscopic retrograde cholangiopancreatography and stent placement (Table 3).

In our case, we achieved a diagnosis of a non-functioning pNET with moderate dysplasia, grade (G2), established on the basis of biopsy (Ki67 > 5%) in a 58-year-old male who refused surgery. We decided to ablate based both on the grading and the age of the patient. Moreover it is worth noting that FNA cytology may underestimate the staging based on surgical specimens. Physicians should be very cautious in using FNA specimens to classify a tumour as low-grade[22]. Consequently our treatment aimed at the complete ablation of the lesion while sparing the pancreatic parenchyma. The nodule we treated had a cystic central component, which has not yet been described in the literature for pNET EUS-guidance ablation. A tecnique similar to that described for cystic neoplasm ablation (ethanol injection and reaspiration) was used.

In conclusion, based on our case study and literature review, we find that this technique is feasible, relatively safe and efficient when applied to symptom relief in functioning tumours. However, the long-term outcomes remain unknown. For non-functioning tumours, it can provide good results for patients unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients is still undefined and larger comparative studies with long-term follow-up are needed to assess its role.

COMMENTS

Case characteristics

The authors describe a procedure of eus guided ethanol ablation along three sessions for a cystic pancreatic neuroendocrine tumours (pNET).

Clinical diagnosis

Incidental focal lesion of the pancreatic tail with endoscopic ultrasound (EUS) "bull's eye appearance" and peripheral hypervascularization, suspicious for neuroendocrine tumour.

Differential diagnosis

Other focal lesions of the pancreas.

Laboratory diagnosis

No lab abnormality including levels of carcinoembryonic antigen and carbohydrate antigen, but recent onset of glucose intolerance.

Imaging diagnosis

Abdominal ultrasound, endoscopic ultrasound, magnetic resonance, EUS guided FNA.

Pathological diagnosis

Neuroendocrine tumor, G2, Ki67 proliferative index > 5%.

Treatment

The authors treated the patient by EUS-guided ethanol injection along three sessions.

Related reports

For patients unfit for surgery due to high-risk comorbidity or for those who refuse resection EUS-guided ethanol ablation has been reported in a few cases.

Term explanation

pNETS: Pancreatic neuroendocrine tumours; EUS: Endoscopic ultrasound.

Experiences and lessons

The authors find that EUS guided ethanol ablation is relatively safe and efficient

for the treatment of pNETs in patients unfit for surgery or for those who refuse surgical resection. Its role in "fit for surgery" patients is still undefined.

Peer-review

A well written paper having a clear endpoint and objectives. The review of the literature is complete and presented in an attractive way.

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