ORIGINAL PAPERS

Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography

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ABSTRACT

Background: the detection and diagnosis of neuroendocrine tumors (NETs) is challenging. Endoscopic ultrasonography (EUS) has a significant role in the detection of NETs suspected from clinical manifestations or imaging techniques, as well as in their precise localization and cytological confirmation using EUS-Fine-needle aspiration-puncture (FNA).

Objective: to assess the usefulness and precision of EUS-FNA in the differential diagnosis and confirmation of NETs, in a retrospective review of our experience.

Patients and methods: in a total of 55 patients with suspected NETs who underwent radial or sectorial EUS, 42 tumors were detected in 40 cases. EUS-FNA using a 22G needle was performed for 16 cases with suspected functional (hormonal disorders: 6 cases) and non-functional NETs (10 cases). Ki 67 or immunocytochemistry (ICC) testing was performed for all.

There was confirmation in 9 cases (5 female and 4 male) with a mean age of 51 years (range: 41-81 years).

All tumors were located in the pancreas except for one in the mediastinum and one in the rectum, with a mean size of 19 mm (range: 10-40 mm).

Results: there were no complications attributable to FNA. Sensitivity was 100% and both precision and PPV were 89%, as a false positive result suggested a diagnosis with NET during cytology that surgery finally revealed to be a pancreatic pseudopapillary solid tumor.

Conclusions: EUS-FNA with a 22G needle for NETs has high sensitivity and PPV at cytological confirmation with few complications.

Key words: Fine-needle aspiration-puncture (FNA) guided by endoscopic ultrasonography (EUS) or echoendoscopy. Neuroendocrine tumors (NETs). Pancreatic endocrine tumors (PETs). Immunocytochemistry. Immunohistochemistry. Chromogranin. Synaptophysin. Cytokeratin 19. Vimentin. Ki 67. CD56.

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INTRODUCTION

The preoperative diagnosis and precise localization of neuroendocrine tumors (NETs), particularly pancreatic NETs (PNETs), is challenging, and vital for a definitive cure of patients (1). For non-functioning cases, confirmation by histology is most necessary because of potential differential diagnoses. PNETs share histological properties with carcinoids: both are considered to derive from the diffuse endocrine cell system; they unusually exhibit mitotic features (assessable using the Ki-67 index); they usually show electrodense granules that contain hormones and various peptides, chromogranins (A, B, C), neuron-specific enolase (NSE), and synaptophysin (2,3).

PNETs are clinically classified as functional (Zollinger-Ellison syndrome, etc.) and non-functional. The clinical diagnosis of functional PNETs is relatively straightforward.

Most are benign (no metastases) and small, and may be associated with multiple endocrine neoplasia (MEN). Non-functional tumors are most common among PNETs, and have a high incidence of metastatic disease.

Their precise localization in the pancreas is difficult. Echoendoscopy or endoscopic ultrasonography (EUS) is a rather recently introduced diagnostic technique, and may diagnose tumors smaller than 1 cm (up to 3 mm) in the pancreas head and body with a sensitivity above 85% (93% in the larger series), whereas those in the tail are harder to assess (1).

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EUS allows fine-needle aspiration-puncture (FNA) under ultrasound (US) guidance (4), and the collection of material for cytology and histology with a yield nearing 90%. In addition, immunocytochemistry (ICC) and immunohistochemistry (IHC) tests may be performed on obtained samples for chromogranin (C-A), synaptophysin, cytokeratin 19, and various hormones or peptides, with diagnoses that may reach 100% for cystic PNETs (5).

A recent classification proposed by WHO (2) assigned three categories to NETs: well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma based on histology, size (limit: 2 cm), and proliferation index (Ki-67 = 2%).

A TNM (tumor, node, and metastasis) classification has also been suggested for PNETs based on the WHO classification (3).

OBJECTIVE

To assess the usefulness and precision of EUS-FNA in the differential and confirmatory diagnosis of NETs using a retrospective review of our team's experience.

PATIENTS AND METHOD

For a total of 55 patients with suspected PNETs who underwent radial or sectorial EUS, 42 tumors were identified in 40 patients. Inclusion criteria for EUS-FNA: patients with presumed NET diagnosis with EUS, uncertain or non-functional.

For 16 cases (8 women and 8 men with a mean age of 56, range: 41-92 years with suspected functional (6 cases) and non-functional (10 cases) tumors, none of them cystic, EUS-FNA was performed using a 22 G needle (Echotip Ultra, Cook Medical) with conventional technique. All cases underwent Ki67 testing or immunocytochemistry for chromogranin, synaptophysin, and various hormones or peptides.

There was surgical confirmation (the gold standard) in 9 patients; in the remaining cases imaging techniques and 12-month follow-up (the gold standard) were used to reach a definitive diagnosis.

From all 16 patients 9 (5 women, 4 men) were selected with a mean age of 51 years (range: 41-81 years).

All tumors were in the pancreas, and one was in the mediastinum and one in the rectum, with a mean size of 19 mm (range: 10 to 40 mm) (Table I).

Regarding pancreatic tumors, three were in the head, two in the tail, and two in the body. Only two patients had metastases.

All examinations (EUS-FNA) were performed after collecting an informed consent, with prior coagulation testing, and using sedation (propofol) by an anesthetist.

A cytologist was in all cases present in the examination room where EUS-FNA procedures were carried out.

Diagnostic precision (P), sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were all analyzed using standard formulas.

RESULTS

There were no EUS-FNA-related complications (hemorrhage and perforation).

In the total series (16 cases) S was 100% with a Sp of 67%, P and PPV of 93 and 92%, respectively.

In patients with surgical confirmation (9 cases) sensitivity (S) was 100%, and precision (P) and PPV were 89%, as cytology yielded a false positive result that was eventually diagnosed as a solid pancreatic pseudopapillary tumor following surgical excision and tail pancreatectomy plus IHC.

DISCUSSION

EUS-FNA has been performed for PNETs for slightly over 10 years now. In earlier works both sensitivity and precision were low, with a specificity of 100% (6); however, they gradually increased, and sensitivity reached about 90% (94% in the most extensive series in the literature) (6-22) (Table II).

Our findings are consistent with those in the literature (S: 100%).

Typical EUS findings include homogeneous pancreatic nodules or lesions that are hypoechogenic, solid, hypervascular, and encapsulated with well-delimited borders (1,22,29), even non-functional ones (most of them) (22). NFPETs show the greatest sizes and are more advanced (Fig. 1).

The use of ICC techniques (chromogranin, synaptophysin, etc.) (cytokeratin 19) (23) considerably improves sensitivity on cytology material (Fig. 2).

The Ki 67 index (24-26) and microsatellite instability have also been assessed in samples (27,28) to establish the benign or malignant nature of tumors, and hence their prognosis.

Algorithms are similar for PNETs and pancreatic cancers (PCs) (4,29) (Fig. 3).

When a tumor is resectable according to computed tomography plus EUS, and both clinical and morphological features are consistent, laparoscopic or open surgery may be readily performed. For uncertain or non-functioning tumors EUS-FNA may be used to confirm diagnostic suspicion.

Sometimes a histological differential diagnosis is difficult between pancreatic endocrine tumors, solid pseudopapillary tumor, acinar cell carcinomas, mucinous tumors, and lymphoma/plasmocytoma. In recent years various cases of solid pseudopapillary tumor have been described where ICC reached the right diagnosis on EUS-

Table I. Case report

N.º	Age/Sex	Diagnosis	Size	FNA	ICC/IHC
1	41/M	Insulinoma, nody-tail:	12-15 mm	FNA +	V + ICC
2	49/M	NF, head	23 x 25	FNA +	V + ICC
3	42/F	PET, tail (pseudopapillary)	12 x 14	FNA +	F + ICC e IHC
4	46/M	PET, tail (Ki 67:10%)	13 x 14	FNA +	V + ICC
5	45/M	I-G, head	40 mm. B	FNA +	V +
6	50/F	Insulinoma, head-body	5.5 x 10.2	FNA +	V +
7	48/M	MEN-1/Uncinate-tail	20 mm	FNA +	V + ICC + Gastro-duodenal < 10 mm: Biopsias + e ICC Ki 67 < 5% Non-op.
8	79/M	NF, head (CT: casual)	12 by 16	FNA +	V + ICQ. No Op.
9	41/F	NF, body (NFM on CT)	12 by 14	FNA +	V + ICQ
10	75/F	Mediastinal (PC) Ki 67 8%	66-70 B	FNA +	V + ICC. Non-op.
11	68/F	Mediastinal (PC)	12-16	FNA +	V + IHC. T4N2
12	81/F	Rectal carcinoid (41) (42)	30 mm B	FNA +	V + ICC
13	55/M	Pancreatic gastrinoma, head	<10 mm	FNA -	No Op.
14	47/F	NF PET US/CT: body	9 mm	FNA -	V - . No Op.
15	45/M	MEN-1/Retro/Ca-body 5-10-20-40		FNA +	V + ICC Gastro-duodenal C-A & serotonin + < 5 mm Non-op.
16	92/F	NF PET on CT, head	23-26 mm	FNA +	V + ICC. Non-op.

NF PET: Non-functional pancreatic endocrine tumor. PC: Pulmonary carcinoid. Non-op.: Non-operated

ICC/IHC:

1. C-A: Chromogranin +
2. Chromogranin +
3. Vimentin +
4. Ki 67 10%
5. Chromogranin, insulin & glucagon +
6. Insulin +
7. Ki 67 < 5%, chromogranin, synaptophysin & gastrin +
8. Synaptophysin, chromogranin, CD 56 & CAM 5-2 +
9. CD 56, synaptophysin & chromogranin +
10. Chromogranin +, Ki 67 8%
11. Chromogranin +
12. Chromogranin +
15. Chromogranin & serotonin +
16. Synaptophysin, CD56, chromogranin & CEA expression, & keratin 5D3.

Table II. Literature overview

Ciaccia 1998 (6)	19 c. TNEs	S: 84% ? 0% F + (Sp: 100%)
Voss 2000	15 c. in 99 patients (15%)	P: 46.7% NET vs. 81% Adenoca.
Gress 2002	1 c. Tattooed insulinoma	
Jhala 2002	9 c. cytology & ICC +	S: 100% (2/2)
Ginès 2002	10 c. with 14 NETs	P: & S: 90% Sp: 100% 7 c. surgical confirmation
Santo 2002	76 c. (47 F)	P: 94% S: 96%
Ardengh 2004	30 c. with 33 NETs	P y S: 83% Sp: 85.7%
Gu 2005	30 c. IHC (C-A) + in all	100%
Chang 2006	9 c. FNA & ICC	89% (8/9)
Baker 2007-8	13 c./ 9 C with ICC (C-A & synaptophysin)	9/9 100%
Pais 2007	76 c. FNA	S: 86%
Jani 2008	41 c. in 4 a. FNA: 8% C, 15% F & 85% NF	
Chatzipantelis-08	48 c. (40/48 ICC: 83%)	83% 7% inadequate
Kongkam 2008	9 c. Qysctic (9%) FNA & ICC + C & S:	100%
Alsohaibani 2008	14 c. EUS: 100%	FNA: 90% (9/10)
Charfi 2009	6 c. Q with ICC + in all	100% (6/6)
Figueiredo 2009	86 c./ 77 c. (90%) FNA & ICC. 9% C & 14% F 100% (10c.)	
Piani 2008	18 c. FNA & Ki 67 < 2%: 89%	
Alesiev 2009	15 c. ICQ & Ki 67	
Chatzipantelis-09	35 c. Ki 67: prognosis marker	
Fasanella 2009 (28)	29 c. Microsatellites. FAL<0.2 benign	
Gornals 2010	16 c (9 with surgical confirmation) PPV: 89% S: 100% (9c.)	
Summary:	> 500 c	P: 81% S: 94% Sp: 95%

Fig. 1. Pancreatic EUS: PET and EUS-FNA.

FNA-collected samples (30-33): most were vimentin+ and cytokeratin+, whereas chromogranin and NSE were negative (they may be focally positive though) (34).

In this multicenter study in 28 patients with pseudopapillary tumors (34) a preoperative diagnosis was reached for 21 cases (75%); vimentin, alfa1-antitrypsin, CD10, and beta-catenin were positive in all cases, whereas chromogranin was positive in just 1/20 (5%) and synaptophysin in 10/17 (59%); however, the best marker to tell endocrine tumors from solid pseudopapillary tumors was E-cadherin/B-catenin/CD10 according to a recent study (35).

In our case with a solid pancreatic pseudopapillary tumor IHC was key for a definitive diagnosis. False positive results have been described in other series (12,18).

A recent Japanese study (36) reviewed 455 pancreatic FNA procedures: 28 were rare pancreatic tumors (no duc-

tal adenocarcinomas). EUS-FNA with cytology, cell-block, and immunocytochemistry correctly diagnosed tumor type in 19 patients 19 (68%).

In differentiating benign from malignant tumors it had a sensitivity of 69%, a specificity of 100%, a PPV of 100%, a NPV of 79%, and a precision of 86%. None of the three malignant pancreatic endocrine tumors was diagnosed as such. EUS-FNA changed the presumed diagnosis in 11 cases (39%).

Four cases have been recently reported (37) where small (8-16 mm), non-functioning pancreatic endocrine tumors were found together with intraductal papillary mucinous neoplasms. PNETs remained undetected by common imaging techniques (CT and MRI); 3/4 were diagnosed using EUS, and only 1/3 using EUS-FNA.

To conclude, ICC on cytology samples collected by EUS-FNA is key for a definitive diagnosis of PNETs. Our study (S: 100%) (PPV: 89%) confirmed the findings in the literature (mean sensitivity of 94%, mean specificity of 95%) (Table II).

Notwithstanding, the diagnostic panel is increasingly greater, and novel markers emerge including SERPINB8 (38), which is as sensitive as C-A and synaptophysin, or CDX-2, PDX-1, NESP-55 and TTF-1, which may help in the differential diagnosis between gastrointestinal and pulmonary carcinoids, and pancreatic endocrine tumors (39), with CK 19 being an independent prognostic factor for PNETs, particularly non-insulinomas according to a recent review (40). However, chromogranin and synaptophysin remain the key markers since many years ago (43) to this day (44).

Thus, believe that ICC is key for a definitive diagnosis of NETs (45), a statement not fully shared by other teams (44).

Fig. 2. ICC: chromogranin A+.

Fig. 3. Algorithm.

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