**Endosonographic and cyst fluid characteristics of cystic pancreatic neuroendocrine tumours: A multicentre case series**

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**Article info**

**Abstract**

*Background:* Pancreatic neuroendocrine tumours are uncommon neoplasms which may rarely be cystic. Differentiation from other more common cystic neoplasms may be difficult.

**Aims:** To describe the morphologic, cytologic, and cyst fluid characteristics of cystic pancreatic neuroendocrine tumours.

**Methods:** Retrospective analysis of consecutive patients referred for endosonographic evaluation of pancreatic cysts at four centres.

**Results:** 27 patients (12 males) with cystic pancreatic neuroendocrine tumours were identified. Prior to endosonography, this tumour was suspected in only 2 patients based on presenting symptoms (7.4%). The median cyst size was 35 mm (range 8–80 mm). Wall thickening was identified in 13 cases. The median carcinoembryonic antigen level was 1.25 (range 0.6–500). Fine needle aspiration cytology in 17 of 24 patients confirmed neuroendocrine tumour (71%). In 8 of 9 patients who had needle targeting of the cyst wall, cytology was consistent with neuroendocrine tumour (88.9%). 18 patients underwent surgical resection.

**Conclusions:** Cystic pancreatic neuroendocrine tumour was rarely suspected, including by cross-sectional imaging. Wall thickening was identified in approximately half of cases on endosonography. Cyst fluid was typically non-viscous with very low carcinoembryonic antigen levels. Targeting the wall during fine needle aspiration had a high diagnostic yield and should be performed.

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1. Introduction

Pancreatic cysts are increasingly being recognised due to the frequent use of cross-sectional abdominal imaging. Endoscopic ultrasound (EUS) and fine needle aspiration (FNA) play an important role in the assessment of pancreatic cysts [1,2]. Pancreatic neuroendocrine tumours (pNETs) are rare, malignant lesions which may rarely be cystic with variable degrees of wall prominence. Cystic pNET may be difficult to distinguish from common cystic lesions such as pseudocysts or mucinous cystic neoplasms [3,4]. Most cystic neuroendocrine tumours are non-functional and may present a diagnostic challenge to the endosonographer. The purpose of this retrospective, multi-centre series is to evaluate the clinical presentation, EUS morphology, cyst fluid analysis, and cytology in a large cohort of cystic pNET cases.

2. Methods

A retrospective review of all patients undergoing EUS evaluation of pancreatic cysts was performed at Yale New Haven Hospital, University of Alabama Hospital, Massachusetts General Hospital, and Abbott Northwestern Hospital from July 2006 to July 2011 to identify patients with pancreatic neuroendocrine tumours. This study was approved by the respective Human Investigation committees. A search was performed at each institution of EUS and/or pathology databases for patients with a “neuroendocrine tumour.” The cytology and surgical pathology were then searched to confirm a diagnosis of “islet cell tumour” or “neuroendocrine tumour.” Patients identified via a surgical pathology database who did not have EUS at the study site were excluded from data analysis. From the patients identified, the study population included those with...
EUS morphology of a cystic or predominantly cystic (if mixed solid-cystic) pancreatic tumour.

Patient and cyst characteristics were retrospectively recorded including age, gender, presenting symptoms, suspicion for cystic pNET prior to and after EUS, and cross-sectional imaging findings [magnetic resonance imaging (MRI), computed tomography (CT), or trans-abdominal ultrasound (US)]. If available for review, EUS findings recorded included mean cyst size, location within the pancreas, wall thickness (specifically focal or concentric), presence of mural nodule, septations, pancreatic ductal dilation or communication, and pancreatic parenchymal echogenicity. FNA data collected included needle size, number of passes, wall targeting, fluid appearance, cytology, and cyst fluid analysis. Immunocytochemistry was not specifically noted. Co-investigators at each study site completed a data sheet to compile the above information, which was collected and analysed by the lead investigator; given the expertise of each endosonographer and the unavailability of archived images, the EUS images were not re-reviewed.

Surgical pathology results were evaluated in the eighteen patients who underwent resection and the diagnosis of neuroendocrine tumour was confirmed. The degree of tumour differentiation was not specifically noted. The remaining patients who did not undergo surgical resection were either lost to follow-up, conservatively managed with serial imaging, or not operative candidates. When definitive surgical pathology was not available, the diagnosis was confirmed via cytology obtained during FNA.

All procedures were performed by experienced endosonographers. EUS was performed with Olympus (GF-UM20, GF-UM130, or GF-UM160) radial or linear (GFUC 140 or GUCT140) echo-endoscopes (Olympus America, Inc., Centre Valley, PA) or with Pentax (EG-3670U RK) radial or linear (EG-3870UL TK) echo-endoscopes (Pentax Medical Co., Montvale, NJ). A cytology technician or cytopathologist was available on-site for preliminary interpretation in all cases.

3. Results

During the study period between July 2006 and July 2011, 27 patients with cystic pNET were identified. Patient and clinical characteristics are summarised in Table 1. The mean age at the time of diagnosis was 60 years; median age 58 (range 34–80). Twelve patients were male (44%). Thirteen patients had pancreatic cysts incidentally detected on cross-sectional imaging and were asymptomatic (48.1%), 11 patients presented with abdominal pain (40.7%), 2 patients had symptoms suggestive of a neuroendocrine tumour – specifically hypoglycaemia with an elevated insulin level in one patient and Cushing’s-type symptoms in another patient (7.4%), and 1 patient presented with pancreatitis. Endoscopists were asked to evaluate their pre-EUS suspicion for cystic pNET based on the patient’s clinical presentation. Only 2 patients were identified (7.4%). Both of the patients with pre-EUS suspicion for pNET had a clinical history suggestive of neuroendocrine tumour. One patient had a family history of MEN syndrome and presented with pancreatitis; the other patient had symptoms of hypoglycaemia. Twenty-one patients had imaging available for review prior to EUS (18 CT, 2 MRI, and 1 US) which led to a radiologist’s diagnosis of cystic pNET in only 1 case (4.7%).

By EUS, the median cyst size was 35 mm (range 8–80 mm); 16 out of 27 patients had cysts <30 mm (59.3%). Ten were located in the head or uncinate of the pancreas (37%) and 17 were located in the body or tail (63.0%). EUS identified 2 cases with additional pancreatic cystic lesions and 1 with liver metastasis, which were not reported on prior cross-sectional imaging. Wall thickening was identified in 13 of 27 cases (48%) (focal (n = 3) and concentric (n = 10)) (Fig. 1). A nodule was identified in 7 cases (range 2.4–8.5 mm). Wall thickening or a nodule was seen in a total of 16 cases (59.3%). Cyst echogenicity was reported as anechoic in 15 cases (2 with debris), cystic and solid in 9 cases, hyperechoic in 3 cases. Septation was seen in 22 cases (81.5%), of which 8 were multilocular. No main pancreas ductal dilation was noted in any cases. Pancreatic ductal communication was identified in 2 cases. The pancreatic parenchyma echotexture was normal in 21 cases (77.8%), heterogeneous in 3 cases, and fatty or hyperechoic in 3 cases. A summary of the endosonographic findings is summarised in Table 2.

24 patients underwent EUS-FNA. Of the three patients who did not undergo FNA, surgical pathology confirmed neuroendocrine tumour. The endosonographers did not specifically note the reason for not performing FNA. A 22 gauge needle was used in 21 cases and a 25 gauge needle was used in 3 cases. A median of 1 pass was made (range 1–7). Nine patients had FNA with targeting of the cyst wall, specifically noted. In 8 out of those 9 patients (88.9%), cytology was consistent with neuroendocrine tumour. In those 9 cases, wall thickening was noted to be focal in 2 cases, circumferential in 4 cases, and a nodule was present in 3 cases. EUS-FNA cytology was diagnostic in 8/9 (88.9%) cases when the wall was targeted (8 NET and 1 non-diagnostic) versus 10/15 (66.7%) cases without wall targeting (9 NET, 5 benign or atypical cells, and 1 adenocarcinoma – final surgical pathology revealed well-differentiated endocrine tumour) (p = 0.35) (Fig. 2).

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>27</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>58 (34–80)</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>“Functional”</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cushing’s symptoms</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Neuroendocrine tumour</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>suspected per symptoms</td>
<td></td>
</tr>
<tr>
<td>Imaging studies (diagnosis)</td>
<td></td>
</tr>
<tr>
<td>Computed tomography</td>
<td>18 (17 pancreatic cyst, 1 pancreatic neuroendocrine tumour) (86)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>2 (1 intraductal papillary mucinous neoplasm, 1 pancreatic cyst) (9.5)</td>
</tr>
<tr>
<td>Trans-abdominal ultrasound</td>
<td>1 (pancreatic cyst) (4.7)</td>
</tr>
<tr>
<td>Neuroendocrine tumour</td>
<td>1 (4.7)</td>
</tr>
</tbody>
</table>

Fig. 1. Endosonographic image of thick walled cyst with central septations and anechoic spaces.
Table 2
Endosonographic features of cystic pancreatic neuroendocrine tumours.

<table>
<thead>
<tr>
<th>Endosonographic features</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean/median size (mm) [range]</td>
<td>28/35 [8–80]</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Body/tail</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Head/uncinate</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Solitary</td>
<td></td>
</tr>
<tr>
<td>Wall thickness</td>
<td>13/27 (48)</td>
</tr>
<tr>
<td>Concentric</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Focal</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Wall nodule</td>
<td>7/27 (26)</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>7/27 (26)</td>
</tr>
<tr>
<td>Echogenicity</td>
<td></td>
</tr>
<tr>
<td>Anechoic</td>
<td>15 (2 with debris)(56)</td>
</tr>
<tr>
<td>Solid + cystic components</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Septation</td>
<td></td>
</tr>
<tr>
<td>Unilocular</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Multilocular</td>
<td>8 (30)</td>
</tr>
<tr>
<td>No septation</td>
<td>5 (18)</td>
</tr>
</tbody>
</table>

Fluid viscosity was reported by the endosonographer as thin/watery (non-viscous) in 22 of 24 cases (92%) and viscous in 2 cases. The colour was clear in 16 cases, bloody in 7, and cloudy in 1. Following EUS, the endosonographer’s suspected diagnosis was reported in 18 cases to include cystic pNET in 9 cases (50%), “malignant cyst” in 6 cases (33.3%), mucinous cystic neoplasm in 2, and side-branch IPMN in 1 case. EUS-FNA in 17 of 24 patients who underwent EUS-FNA confirmed neuroendocrine tumour (71%) (Fig. 3). CEA and amylase levels were reported in 12 cases with a median of 1.25 (range 0.6–500); only 2 patients had CEA >192 ng/mL. Median amylase level was 84 (range 14–191,037); only 4 cases had amylase >350 U/L. The FNA findings are presented in Table 3. There were no endoscopic complications noted. 18 patients had surgical resection which demonstrated neuroendocrine tumour on surgical pathology in all cases.

4. Discussion

The widespread use of high resolution cross-sectional imaging has led to the increased recognition of pancreatic cysts, with a recent series identifying cysts in 2.4% of the population [5]. EUS plays an important role in the evaluation of pancreas cysts. Mucinous cystic neoplasms are the most common cysts, which are incidentally detected [6,7]. Pancreatic neuroendocrine neoplasms, on the other hand, are rare with an annual incidence in the United States of 4–5 cases per million [8], and may rarely present as cystic lesions. Cystic pNETs are associated with MEN syndrome (present in one patient in our series) and with von Hippel-Lindau and Wermers syndromes [9]. The median age of presentation is between 45 and 60 years [10–12]. Microcystic degeneration of large solid pNETs may occur; however, they may also present as thin-walled cysts which may be morphologically indistinguishable from mucinous cystic neoplasms or contain variable degrees of focal or concentric wall thickening [13,14]. Prior series have demonstrated the malignant potential of CNETs [15–17]. This is the largest series of cystic pNET reported to date with the inclusion of comprehensive EUS morphology, cyst fluid analysis, and cytology. A high degree of suspicion is required among endosonographers to recognise cystic pNETs. Cystic pNETs are typically nonfunctional [12], and the presence of symptoms is not a reliable indicator. Only two patients in our series had functional tumours. Thus, pre-EUS suspicion for cystic pNET by endosonographers was only 7.4% in our series and 4.7% by radiologists, in comparison to 25–40% in prior reports [10,11]. While 41% of patients in our series presented with abdominal pain, the relationship of symptom to the cystic NET is uncertain.

The majority of cystic pNET in our series were solitary and located in the body or tail of the pancreas. Most cysts contained

![Fig. 3. Cyto morphologic features of pancreatic endocrine neoplasm. The on-site Diff-Quick stain from a fine needle aspirate shows clusters of relatively uniform epithelial cells with eccentrically located round to oval nuclei.](image)

![Fig. 2. Endosonographic image of predominantly thin walled cyst with area of focal wall thickening inferiorly that is targeted with fine needle aspiration.](image)

Table 3
Cyst fluid characteristics of cystic pancreatic neuroendocrine tumours.

<table>
<thead>
<tr>
<th>Cyst fluid features</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients undergoing cyst fluid aspiration</td>
<td>24</td>
</tr>
<tr>
<td>Fluid consistency</td>
<td></td>
</tr>
<tr>
<td>Thin</td>
<td>22 (92)</td>
</tr>
<tr>
<td>Viscous</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Fluid colour</td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>16 (67)</td>
</tr>
<tr>
<td>Bloody</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Cloudy</td>
<td>1 (4)</td>
</tr>
<tr>
<td>CEA (median) [range]</td>
<td>1.25 (0.6–500)</td>
</tr>
<tr>
<td>Amylase (median) [range]</td>
<td>84 (14–191,037)</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumour</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Adenocarcinoma*</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Atypical cells</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Benign or no malignant cells</td>
<td>5 (21)</td>
</tr>
</tbody>
</table>

* Confirmed neuroendocrine tumour on surgical pathology.
septations, with normal surrounding pancreas parenchyma and a normal main pancreas duct, consistent with previous reports [12,14].

Targeting of mass lesions, mural thickening or nodules is generally advised with the performance of FNA of cystic lesions [18]. We recognised wall thickening in 13 of 27 cases (48%) and wall nodularity in 7 cases (26%; size range 2.4–8 mm).

With targeting of the wall there was a trend towards a higher diagnostic yield of EUS-FNA cytology (88.9% versus 66.7% without wall targeting). Our series is similar to prior reports with smaller numbers of patients in identifying pNET cyst fluid as clear or serosanguinous, non-viscous and with typically low CEA and amylase levels [12]. It should also be noted that cyst fluid chromogranin A levels have been reported to support the diagnosis of neuroendocrine tumour [19]. In our series, when adequate cellularity was present in the cell block, immunocytochemistry demonstrated high accuracy in confirming the diagnosis of neuroendocrine tumour. Our experience further emphasises the importance of targeting the cyst wall with FNA (even in the absence of wall thickening) as reliance on cyst fluid cytology and CEA alone may erroneously indicate a benign/non-mucinous cyst. Of note, in one case in our series, the initial cytology of the cyst fluid was non-diagnostic without wall targeting and a repeat EUS/FNA with wall targeting revealed NET.

Limitations of our study include the retrospective review and a lack of uniform reporting of EUS morphologic characteristics. Immunocytochemistry was not specifically included in the collaborative analysis as it was not uniformly utilised or recorded at all study sites often due to insufficient cellularity.

In summary, cystic pNET may present a diagnostic challenge as most patients are asymptomatic and the morphologic features may be indistinguishable from more common pancreas cystic neoplasms on advanced imaging and EUS. In our series, cystic pNET was rarely suspected by cross-sectional imaging and approximately forty percent of the patients did not have cyst wall thickening or nodularity. Cystic pNET fluid is typically non-viscous with a low CEA, which may erroneously suggest a benign lesion, in this potentially resectable malignancy. Targeting of the wall should be performed during FNA to maximise diagnostic yield.

Conflicts of interest
The authors have no conflicts of interest to disclose.

References