Original Article

Fluid analysis prior to surgical resection of suspected mucinous pancreatic cysts. A single centre experience

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ABSTRACT

Objective: EUS-FNA cytology and fluid analysis are frequently utilized to evaluate pancreatic cysts. Elevated cyst fluid CEA is usually indicative of a mucinous pancreatic cyst but whether CEA or amylase values can subclassify various mucinous cysts is unknown. The purpose of this study is to determine whether cyst fluid CEA and amylase obtained by EUS-FNA can differentiate between mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs).

Methods: Using our prospective hospital EUS and surgical databases, we identified all patients who underwent EUS of a pancreatic cyst prior to surgical resection, in the last 10 years. Cysts were pathologically sub-classified as MCNs or IPMNs; all other cysts were considered non-mucinous. Values of cyst fluid CEA and amylase were correlated to corresponding surgical histopathology and compared between the two groups.

Results: 134 patients underwent surgery for pancreatic cysts including 82 (63%) that also had preoperative EUS. EUS-FNA was performed in 61/82 (74%) and cyst fluid analysis in 35/61 (57%) including CEA and amylase in 35 and 33 patients, respectively. Histopathology in these 35 cysts demonstrated nonmucinous cysts in 10 and mucinous cysts in 25 including: MCNs (n=9) and IPMNs (n=16). Cyst fluid CEA (p=0.19) and amylase (p=0.64) between all IPMNs and MCNs were similar. Between branched duct IPMNs and MCNs alone, cyst fluid CEA (p=0.34) and amylase (p=0.92) were also similar.

Conclusion: In this single center study, pancreatic cyst fluid amylase and CEA levels appeared to be of limited value to influence the differential of mucinous pancreatic cysts. Larger studies are recommended to evaluate this role further.

KEY WORDS pancreatic cysts; EUS; FNA; amylase; CEA

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Introduction

Mucinous pancreatic cysts are premalignant or malignant pancreatic neoplasms. They usually are asymptomatic and increasingly found due to widespread use of cross-sectional abdominal imaging (CT scan and MRI). Radiologic features of mucinous cysts are often not distinguishable from pseudocysts (PCs) or other cystic neoplasms with minimal malignant potential such as serous cystadenomas (SCAs) (1).

Mucinous pancreatic cysts are classified as mucinous cystic neoplasms (MCNs with or without carcinoma) and intraductal papillary mucinous neoplasms (IPMNs). The latter are further classified into whether the neoplasm involves the main pancreatic duct alone (main duct IPMN), main pancreatic duct side branches alone (branched IPMN), or both the main pancreatic and its side branches (mixed IPMN). The grade of dysplasia in mucinous pancreatic cysts is further classified as low grade dysplasia, high grade dysplasia or invasive carcinoma (2).

Endoscopic ultrasound (EUS)-guided fine needle aspiration (EUS-FNA) cytology with cyst fluid analysis

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is frequently utilized to aid in classification of pancreatic cysts. However, the value of cytology is limited by the frequently low cellularity of aspirated fluid (1). The utility of several cyst fluid tumor markers studied has been variable (3). Brugge et al. concluded that a cyst fluid CEA level of 192 ng/ml has the greatest area under the curve (AUC) for differentiating mucinous from nonmucinous cysts (4). In a pooled analysis of twelve studies, amylase <250 U/L from cyst fluid was found to virtually exclude a pseudocyst. The same study concluded that a CEA of <5 ng/ml and a CEA >800ng/ml was strongly suggestive of a nonmucinous cyst and mucinous cyst, respectively (5).

Combining clinical presentation with EUS morphology and cyst fluid CEA concentration enhances the sensitivity of differentiating mucinous from nonmucinous cysts (4). However, planning appropriate management strategy often requires further classification of various types of mucinous cysts (MCNs vs. IPMNs), particularly in asymptomatic individuals with an increased surgical risk. For example, surgical resection of all MCNs and main duct IPMNs in surgically fit patients is recommended due to a significant risk of malignant transformation. However, there is increasing evidence that branched-duct IPMNs (BD-IPMNs), which are typically found in elderly individuals, have less potential risk of malignancy. Therefore these tumors are often monitored with surveillance imaging without the need for surgical intervention (6,7).

It is not currently known whether pancreatic cyst fluid markers can reliably distinguish between the various subtypes of mucinous pancreatic cysts. The aim of the current study is to determine whether pancreatic cyst fluid CEA and amylase concentrations obtained by EUS-FNA can differentiate either: 1) MCNs from IPMNs or; 2) MCNs from BD-IPMNs.

Materials and Methods

Study population

This study was approved by the Institutional Review Board of Indiana University Medical Center/Clarian Health Partners. Using our prospectively maintained hospital EUS and surgical databases, consecutive patients who underwent EUS prior to surgical resection of a pancreatic cyst over a 10 year period were identified. Hospital records, endoscopy, histopathology, and surgical reports of these patients were reviewed retrospectively. The following clinical information was abstracted: age, gender and symptoms. EUS features of pancreatic cysts noted included the location (head, body, tail, multifocal), number and size of the cysts, communication with the main pancreatic duct or side branch, mural nodules, presence of septation, any associated solid mass. A dilated main pancreatic duct was defined as greater than 3 mm, 2 mm, and 1 mm in the head, body and tail, respectively. EUS-FNA puncture site, number of passes, needle size, cytology results, and cyst fluid carcinoembryonic antigen (CEA), and amylase were noted. The type of surgery and final surgical histopathology findings were also recorded.

Endoscopic ultrasound examination

After written informed consent was obtained, patients received moderate or deep sedation using various combinations of intravenous midazolam, meperidine, fentanyl, or propofol under appropriate cardiorespiratory monitoring. In accordance with a hospital-approved deep sedation policy, registered nurse-administered propofol sedation (NAPS) was available in our endoscopy for all patients beginning in 2001 (8). During the second half of the study period, commencement of deep sedation was usually initiated with a combination of midazolam and meperidine or fentanyl in order to minimize total requirements of propofol (9). The choice of moderate or deep sedation was made at the discretion of the endosonographer. All procedures were performed by or under the supervision of one of six experienced attending endosonographers. EUS examinations were usually initiated with an Olympus GF-UM20, GFUM-130 or GF-UM160 radial echoendoscope (Olympus America, Inc., Center Valley, PA, USA). Curvilinear array endosonography was performed using the Pentax 32-UA, Pentax 36-UX (Pentax Medical Co, Montvale, NJ, USA), Olympus GF-UC30P, or Olympus GF-UC140P-AL5 (Olympus America, Inc., Center Valley, PA, USA) echoendoscope. EUS-FNA was generally performed only if the cyst size was ≥10 mm and if the endosonographer believed that information gained from cyst fluid analysis would impact patient management. FNA was obtained using a 22-gauge EUSN-1, EUSN-2, EUSN-3, or Echotip Ultra needle (Cook Medical Inc., Winston-Salem, NC, USA) or EZ-Shot needle (Olympus America, Inc., Center Valley, PA, USA). Doppler examination was used to ensure the absence of intervening vascular structures along the anticipated needle path. Depending on the amount of blood anticipated during tissue sampling, full or partial suction was applied. In general, a single EUS-FNA pass was performed from the cyst but was repeated if the endosonographer felt that further sampling would increase the yield. Samples aspirated were expressed onto a glass slide and two smear preparations were made. One slide was air-dried and stained with a modified Giemsa stain for rapid on-site interpretation, while the other slide was alcohol-fixed and stained by the Papanicolaou method. A cytopathologist was available on-site for preliminary diagnostic

interpretations and assessment of specimen adequacy on all procedures. If at least 1 ml of fluid was obtained from the aspirate, analysis for carcinoembryonic antigen (CEA) and amylase was requested. Definitive cytopathologic diagnoses were given only after complete staining and subsequent final interpretation was provided. One dose of intravenous antibiotics (i.e. ampicillin/sulbactam or a fluoroquinolone) was given immediately following the procedure followed by 3-5 days of oral antibiotics (i.e. amoxicillin/clavulanate or a fluoroquinolone) if EUS-FNA was performed. Per department policy, all patients were telephoned within 48 hours after the procedure to assess for any short-term complications.

Surgery and surgical pathology

All surgical consultations and operations were performed by 1 of 5 experienced pancreatobiliary surgeons. Decisions for surgery were based on a preoperative evaluation of the patient's fitness for operation coupled with the results of all preoperative imaging studies. All patients had complete abdominal exploration by laparoscopy or laparotomy to rule out metastatic or locally advanced disease. A standard pancreaticoduodenectomy or pylorus-preserving variant was done for lesions located in the head or uncinate process. A distal pancreatectomy and/or splenectomy were done for tumors located in the body or tail. When tumors are resected; routine intraoperative histologic frozen section examinations were done on the pancreatic, bile duct, and retroperitoneal soft tissue margins. A positive pancreatic or bile duct margin for malignancy mandated further resection until a negative margin was obtained. Persistently positive pancreatic margins for malignancy or main duct IPMN often resulted in a total pancreatectomy at the discretion of the surgeon. Regional lymph nodes routinely resected en bloc with the tumor specimen.

The final diagnosis in each patient was made by the result of surgical resection and corresponding histopathology. Histologic interpretation of resected specimens was carried out by experienced gastrointestinal pathologists and interpretation of the cystic lesions was made according to WHO tumor classification as follows: "(1) a mucinous cystic neoplasm (Low Grade Dysplasia (LGD), High Grade Dysplasia (HGD), or malignant) or (2) a nonmucinous cystic lesion including serous, inflammatory, and endocrine. Cystic lesions arising from an intraductal papillary mucinous tumor (IPMN) were considered mucinous" (10).

IPMNs were further classified as branched cysts only (BD-IPMN) or involving the main pancreatic duct with or without side-branched cysts (MD-IPMN). Malignant mucinous cysts demonstrated were defined as the presence of invasive carcinoma; all other neoplasms (including high grade dysplasia) were considered benign.

Statistical analysis

Continuous variables associations were assessed with an unpaired *t* test. The association between categorical variables of mucinous and non mucinous cysts was assessed with the Fisher's exact test. Mean values of cyst fluid CEA (normal range 0-2.5 ng/ml) and amylase (normal range 25-115 U/L) were correlated to corresponding surgical histopathology and compared using the Mann-Whitney Test. A *p*-value less than 0.05 was considered statistically significant.

Results

During the study period, 134 patients underwent surgery for pancreatic cysts including: 87 (65%) classic or pylorus sparing pancreaticoduodenectomies, 44 (33%) distal pancreatectomies and 3 (2%) total/subtotal pancreatectomies. Of these, 82 (61%) patients (28 male; median age 60 years; range; 20-83) patients had a preoperative EUS and comprised the study population (Figure 1). No EUS-related complications were noted in any patient.

Surgical pathology revealed 66 mucinous and 16 non-mucinous pancreatic cysts (Table 1). Although age was similar between the two groups (p=0.51), mucinous cysts were significantly more common in females (p=0.04). No statistically significant difference in any presenting symptom was noted between the two groups. Abdominal pain was the most common presenting symptom (n=42,

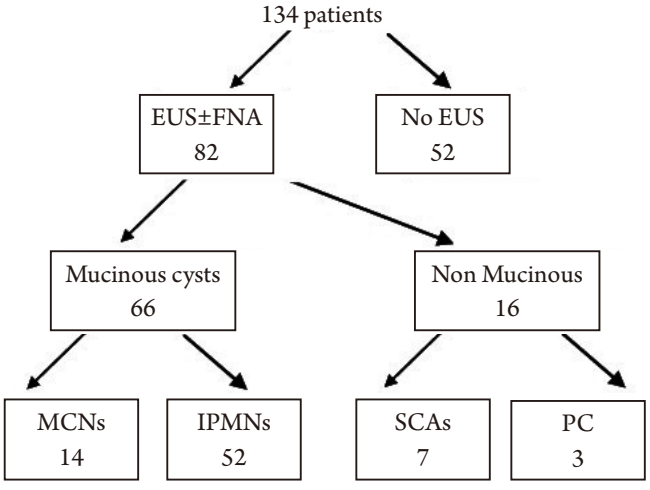

Figure 1 Algorithm of study population. MCN: mucinous cystic neoplasm; IPMN: intraductal papillary mucinous neoplasm; SCA: serous cystadenoma; PC: pseudocyst.

Table 1 Clinical and demographic features of 82 pancreatic cysts undergoing surgical resection following EUS

Characteristics	Mucinous (n=66)	Non-Mucinous (n=16)	*p*-value
Clinical			
Age (mean ± SD), yrs	60 ± 13	58 ± 11	0.51
Gender (n, %)			
Male	18 (27)	10 (62)	0.19
Female	48 (73)	6 (38)	0.04
Abdominal pain (n, %)	28 (42)	14 (88)	0.05
Preceding pancreatitis (n, %)	18 (27)	6 (38)	0.23
Weight loss (n, %)	12 (18)	3 (18)	0.35
Incidental (n, %)	7 (10)	2 (12)	0.18
Jaundice (n, %)	5 (8)	1 (6)	0.22
Diarrhea (n, %)	3 (5)	1 (6)	0.60
Back pain (n, %)	2 (3)	3 (18)	1.00
Cyst Location			
Head/Neck (n, %)	51 (77)	5 (31)	0.001
Body (n, %)	5 (8)	3 (19)	0.70
Tail (n, %)	7 (10)	7 (44)	1.00
Multifocal (n, %)	3 (5)	1 (6)	0.60
Type of Surgery			
Pancreaticoduodenectomy (n, %)	44 (67)	4 (25)	0.001
Distal Pancreatectomy (n, %)	21 (32)	11 (69)	0.11
Total / subtotal pancreatectomy (n, %)	1 (1)	1 (6)	1.00

58%), followed by preceding history of pancreatitis (n=24, 33%). Nine patients (7 mucinous and 2 non-mucinous) were asymptomatic with a cyst found incidentally on abdominal cross-sectional imaging done for other indications. Mucinous tumors originated more often from pancreas head and neck (p=0.001), and therefore were more likely to require pancreaticoduodenectomy (P=0.001).

Final pathology from the 66 resected mucinous cysts undergoing preoperative EUS included 14 MCNs and 52 IPMNs. None of the MCNs had high grade dysplasia (HGD) or cancer. Pathology from the 52 IPMNs included: low grade dysplasia (LGD) in 37, HGD in 7, and invasive cancer in 8. EUS-FNA (Table 2) was performed in 61/82 (74%), including 16 of 16 (100%) of the non-mucinous cysts and 45 of 66 (68%) mucinous tumors. Cyst fluid analysis was feasible in 35/61 (57%) patients, including CEA and amylase levels in 35 and 33 patients, respectively (Table 3). Histopathology in these 35 pancreatic cysts demonstrated 10 non-mucinous cysts and 25 mucinous cysts.

The 10 non-mucinous cysts included 7 serous cystadenomas (mean CEA = 4272 ng/ml, median CEA = 92 ng/ml; range: 0.5 – 22343 ng/ml; mean amylase = 3209 U/L, median amylase = 1111 U/L; range: 350-14670U/L) and 3 pseudocysts (mean CEA = 177 ng/ml, median CEA = 93; range 1.7-410 ng/ml; mean amylase = 28610 U/L, median amylase 28208 U/L; range 19834-37789 U/L).

The 25 mucinous cysts included 9 MCNs (mean CEA = 21119 ng/ml, median CEA 813 ng/ml; range 1.3-181196 ng/ml; mean amylase = 45567 U/L, median amylase = 31437 U/L; range 28-162400), 11 IPMN-Br (including one cancer and 5 HGD; mean CEA = 613 ng/ml, median CEA = 426 ng/ml; range 3.8-4878 ng/ml, mean amylase = 25641 U/L, median amylase = 744 U/L; range 223-122532 U/L) and 5 IPMN-M (including one cancer; mean CEA = 143 ng/ml, median CEA 181 ng/ml; range 43-298 ng/ml, mean amylase = 67763 U/L, median amylase = 14580 U/L; range 744-108451 U/L).

Mean CEAs were greater for mucinous compared to non-mucinous cysts, however there was no statistically significant difference in cyst fluid amylase levels between the two groups (Table 3). Comparison between cyst fluid CEA and amylase for all 25 mucinous cysts are shown in the Table 4. As shown, cyst fluid CEA (p=0.34) and amylase (p=0.92) were also similar between BD-IPMNs and MCNs alone.

Discussion

Pancreatic cysts are increasingly detected due to widespread

Table 2 Results of EUS-FNA cytopathology for cystic tumors confirmed by surgical pathology

1-Cytology of Mucinous cysts (n=45)	n (%)
Adenocarcinoma	3 (6)
Extracellular mucin	6 (13)
IPMN	7(16)
Non diagnostic	9 (20)
Benign cells	14 (31)
Atypical cell/suspicious for neoplasm	4 (9)
Mesothelial cells	2 (5)
2-Cytology of non Mucinous cysts (n=16)	
Benign cyst	8 (50)
Macrophages/benign cells	4 (25)
Non diagnostic	2(13)
Suspicious for neoplasm	1(6)
Chronic pancreatitis	1(6)

Table 3 EUS-FNA cyst fluid analysis

Cyst fluid result	Histopathology		*p*-value
	Non-Mucinous (n=10)	Mucinous (n=25)	
Mean CEA (SD)	3792 (9089)	7602 (35428)	<0.01
Median CEA (range)	50 (0.5 – 22343)	206 (0.8 – 181196)	
Mean amylase (SD)	30735(48858)	37285(38455)	0.34
Median amylase (range)	15531 (350 – 37789)	22194 (28 - 122532)	

CEA: carcinoembryonic antigen (normal value 0-2.5 ng/ml). Amylase (normal value 25-115 U/L).

Table 4 Cyst fluid analysis of Mucinous cysts

Cyst fluid result	Histopathology		*p*-value
	MCN (n=9)	IPMN (n=16)	
Mean CEA (SD)	21119 (60045)	466.3 (1190)	0.19
Median CEA (range)	813 (0.8 – 181196)	144.5 (0.8 – 4878)	
Mean amylase (SD)	45567 (56237)	42280 (38790)	0.64
Median amylase (range)	31437 (28 – 162400)	32154 (223 – 122532)	

MCN: mucinous cystic neoplasm; IPMN: intraductal papillary mucinous neoplasm; CEA: carcinoembryonic antigen.

use of cross sectional imaging like CT scan and MRI. The majority of pancreatic cystic lesions are benign such as pseudocysts and serous cystadenomas. However, it is estimated that 10-15% of pancreatic cysts are potentially premalignant or malignant cystic neoplasms, (usually mucinous cysts) that require further evaluation, management and follow up (1,11). EUS has emerged as the preferred modality to study these lesions because it provides high resolution images and morphologic detail compared to other imaging techniques. EUS-FNA also permits collection of cyst fluid for analysis for diagnostic markers such as CEA, CA19-9, CA 72-4, CA-125, amylase, and lipase to help differentiate among different types of pancreatic cysts (12). A cyst fluid CEA of 192 ng/ml appears to optimize the diagnosis of mucinous with non-mucinous tumors (4). However, it is not known whether pancreatic cyst fluid markers can reliably differentiate one type of mucinous pancreatic cyst from another.

In the present study, we performed a cohort analysis of cyst fluid markers in patients who underwent EUS-FNA prior to surgery to investigate whether cyst CEA and/or amylase levels would aid in the differential diagnosis of various types of mucinous cysts. Sixty-six of the 82 (80%) patients in the study population who underwent surgery had

pathologically confirmed mucinous lesions and a variant of IPMN were found in 52 (63%). Clinical symptoms at presentation did not vary significantly between mucinous and non-mucinous cysts and similar to prior reports, females were more commonly found to have mucinous compared to nonmucinous cysts (2,13).

Cyst fluid analysis was feasible in 43% of our cohort. Similar to previous reports, we found that cyst fluid CEA was significantly higher in mucinous compared to non-mucinous lesions. However, amylase was similar between the two groups (p=0.34). Amylase is reportedly elevated in cyst fluid that communicates with the pancreatic ductal system, such as pseudocysts and IPMNs. However, cyst fluid amylase is not typically elevated in tumors with only rare ductal communication such as SCAs or MCNs (14,15). Since most mucinous cysts in our series are of the IPMN type, a significant overlap in the amylase value could explains the lack of differentiation of this marker among various cyst types.

We also found that cyst amylase and CEA are similar among BD–IPMNs and MCNs. This is clinically relevant since these two types of mucinous cysts with normal diameter main pancreatic ducts may be difficult to differentiate by morphologic imaging alone. Current guidelines recommend surgical resection for MCNs but recent data suggest that BD-IPMN smaller than 3 cm without referable symptoms or recent enlargement may be followed clinically (16). Our data suggest that cyst fluid CEA and amylase cannot be used to distinguish these two groups. Prior smaller studies have shown variable results (17-19). Khalid et al. have shown that DNA analysis can point to a mucinous lesion when there is uncertainty from the CEA analysis alone. However, the same study has not proven that DNA analysis can help distinguish BD-IPMN from MCNs (3).

The current series is an additional demonstration of the clinical challenge to accurately predict cyst pathology in order to plan proper patient management. While there is an increasing interest in non-surgical management of many neoplastic cysts (20,21), the precise preoperative diagnosis is crucial (6,22). Recently developed molecular analyses of cyst fluid may provide a promising role in distinction of nonmucinous from mucinous cyst in general and of benign and malignant cysts in particular (3,23).

This series has a few limitations that merit discussion. This is a retrospective study from a single tertiary referral center and thus could have been underpowered to detect a true difference in CEA levels between the two cyst types studied. Only 61% of all resected pancreatic cysts during the study period had preoperative EUS evaluation, and more than half of the cases did not undergo EUS-FNA. This could be explained by the fact that the decision to resect many of the pancreatic cysts especially the large ones which may have been symptomatic then was based on conventional imaging features as well as the clinical presentation; therefor EUS with fluid aspiration results may not have felt to influence the treatment course and therefore were not referred for preoperative EUS evaluation. Of those who underwent FNA, cyst fluid analysis was technically not feasible in about one-third of patients, due to technical reasons or small fluid volume amenable for adequate laboratory testing. Thus, type I error and referral bias is expected since most surgeries in this series were performed for malignant or highly suspicious premalignant lesions.

In conclusion, the current series suggest that pancreatic cyst fluid amylase and CEA levels may not appear to distinguish BD-IPMNs from MCNs. However; larger adequately powered studies are needed to evaluate this further. Therefore, clinical picture, cyst imaging morphology and evaluation of the presence (IPMN) or absence (MCN) of pancreatic duct communication remains the up-to-date tools to differentiate these two groups.

Conflict of Interest

The authors have no conflict of interest to declare related to this work.

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