Mucin Expression in Mucinous Pancreatic Cysts: Can String Sign Test Predict Mucin Types? A Single Center Pilot Study

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ABSTRACT

Background: *Mucinous pancreatic cystic lesions (PCLs) express different mucin (MUC) types according to their histomorphologic types. High cystic fluid viscosity may help in the detection of mucinous PCLs. We hypothesized that high cystic fluid viscosity may be suggestive of a certain MUC type in mucinous PCLs.*

Methods: *Prespecified MUC types (MUC1, MUC2, MUC4, MUC5AC, and MUC6) were evaluated in 18 definitively diagnosed mucinous PCLs with sufficient tissue material and prediagnostic cyst fluid viscosity evaluation—string sign (SS)—test. We evaluated the agreement of MUC expression with positive SS test results. Later, we compared cystic fluid carcinoembryonic antigen (CEA) between the prespecified MUC expressing and nonexpressing cyst types.*

Results: *A total of 18 mucinous PCL patients, 11 females, with mean age ± SD (59.7 ± 13.3) were included. Almost all malignant mucinous PCLs expressed MUC1 (71.4%) (P = .023). We found no significant agreement between the prespecified MUC types and positive SS, except MUC4 which had mild agreement. Also, no significant relation was found between cystic fluid CEA levels and MUC expression (P = .584).*

Conclusion: *We did not detect a significantly moderate or good agreement between the prespecified MUC types and SS test. MUC1 was highly expressed in malignant mucinous cysts; however, it was incompatible with the SS test. MUC4 expression showed mild agreement with the SS test in a small number of patients.*

Keywords: *String sign, pancreas cyst, MUC, malignancy*

INTRODUCTION

Mucinous pancreatic cystic lesions (PCLs) are one of the most challenging to diagnose due to their malignancy potential. Mucinous PCLs include intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), intraductal oncocytic papillary neoplasms, cystic changes in ordinary ductal adenocarcinomas, and other invasive carcinomas, such as cystic pancreatic ductal adenocarcinoma (PDAC).[1] Such cystic lesions are mostly incidentally detected by cross-sectional imaging in recent decades.Differentiation of benign from early malignant cysts is difficult in most patients because there is no single criterion or follow-up model for a definitive diagnosis or surveillance of malignant potential harboring mucinous PCLs in the preoperative period.[2] On the other hand, unnecessary surgery may increase morbidity and mortality.[3] Endosonographic (EUS) evaluation with fine-needle aspiration (FNA) is important in diagnosis and follow-up of mucinous PCLs. Cyst fluid viscosity, carcinoembryonic antigen (CEA), and cytological features are very important in the diagnosis and in surgery decision of mucinous PCLs.[4,5]

Recently, there is an increase in the data on the role of mucins (MUC) in the pathogenesis of pancreatic malignancies. MUC are a heterogeneous family of glycoproteins with different expression profiles in mucinous PCLs. Today about 21 MUC types are known. MUC can be classified as secreted (MUC2, MUC5AC, and MUC6) and membrane-bound or transmembrane mucins (MUC1, MUC4, and MUC16) according to their structural and functional properties.[6,7]

String sign (SS) method is highly specific and a simple method for predicting mucinous PCLs, which depends on the stretching ability of the cyst aspirate due to the mucus content.[8] To the best of our knowledge, there is no report evaluating the compatibility of MUC expression

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with positive SS. Thus, according to our hypothesis, if SS positivity is based on a specific MUC type, in this case, by looking at the positivity of SS, we can estimate the MUC type secreted by the pancreatic cyst. Therefore, we aimed to evaluate the relationship between certain available MUC expression types (MUC1, MUC2, MUC4, MUC5AC, MUC6) and positive SS.

MATERIALS AND METHODS

Study Design and Participants

We retrospectively analyzed the data of 466 PCL patients who underwent EUS-FNA between 2011 and 2018. Of these, 102 (21.8%) were definitively identified as mucinous PCLs cytopathologically. We retrospectively reviewed the prospectively collected database of pancreatectomies or cytologic materials performed at our hospital.

We reviewed the cytopathological specimens of patients for immunohistochemical work-up who had previous SS testing during EUS-FNA. We investigated the compatibility of SS test with the available prespecified MUC types (MUC1, MUC2, MUC4, MUC5AC, and MUC6) in 18 patients.

We gathered demographic data, EUS evaluation, SS testing results, cyst fluid CEA level, cytopathology results, and surgical history from electronic medical records. For classification purposes, patients were grouped as benign (low-grade dysplasia and borderline) or malignant (high-grade dysplasia, invasive cancer, and PDAC) according to their histopathologic diagnosis.[9]

This study was approved by the Institutional Review Board (IRB No: 15/170).

EUS Methods

All EUS procedures were performed by a single operator after obtaining informed patient consent. EUS procedures were performed by a linear echoendoscope (Pentax; A121091, H121645, H121435, H121637 Pentax Medical Co, Montvale, NJ, USA, Fujinon K1U047K062). EUS-FNA was carried out by a single passage using either a 22 or 19 gauge needle (Cook Medical, Boston Scientific). A single dose of prophylactic intravenous antibiotics was administered after cyst aspiration. A cyst fluid sample was sent for cytological analysis and for the determination of CEA and amylase in those with sufficient cyst fluid.

Cyst Fluid CEA Analysis

CEA levels aspirated from the cyst fluid were measured by a carbonylmetallo-immunoassay kit (Abbott Core Laboratory, Architect i2000SR, Abbott Park, IL, USA). A minimum of 0.3 mL aspirate was necessary.

Viscosity Evaluation-SS Test

Viscosity-SS testing was measured by the endosonographer immediately after EUS-FNA by placing the cyst aspirate on a slide, touching the fluid with a gloved finger and slowly stretching the fluid across the glass with the index finger. Viscosity measured by the maximal length of mucus string is considered positive if the aspirated fluid stretches along the slide (forming a "string") for at least 10 mm for more than 1 second.[8] SS test was considered negative if the aspirated fluid did not stretch but remained round, like a droplet.

Cytology

All cytological analyses were carried out or reviewed by the study cytopathologist. Samples were reported to be diagnostic or nondiagnostic. Diagnostic samples were considered to have a mucinous epithelium. Nondiagnostic samples contained either a nonmucinous epithelium or no epithelial cells. The mucinous epithelium was graded according to epithelial atypia as low risk (LR) (LGD/IGD) or high risk (HR) (HGD/invasive carcinoma).[9]

Histology

Histologic diagnostic sources were from surgical resections. The resection cohort included MCNs and IPMNs with histologic diagnosis. All histological analyses were carried out or reviewed by the study pathologist. Ovarian-type stroma was required for the diagnosis of MCNs. The surgical specimens were categorized according to the World Health Organization classification system.[9,10] MCNs and IPMNs were categorized as LR (low- and intermediate-grade dysplasia in surgical materials), and HR (high-grade dysplasia and invasive carcinoma in surgical materials).

Immunohistochemical Evaluation-MUC Expression

Immunohistochemical staining was performed using 4-μm tissue sections from the same formalin-fixed, paraffin-embedded tissue block (either from the resection material or the cell block) selected for initial hematoxylin and eosin examination. Staining with MUC 1 (MUC1/EP85, 1:100; Cell Marque, Rocklin, CA, USA), MUC 2 (Cell Marque MUC2/MRQ18; 1:100), MUC 4 (Cell Marque MUC4/8G7; 1:100), MUC 5AC (Cell Marque MUC5A/MRQ-19; 1:100), and MUC 6 (Cell Marque MUC6/MRQ-20; 1:100) was performed in all cases. Immunostaining was performed using appropriate controls and was reviewed by the study cytopathologist.

Statistical Analyses

Statistical analyses were conducted using the IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms/probability plots) and analytical (Kolmogorov–Smirnov test) methods to determine whether the results were normally distributed. Data are shown as mean ± standard deviation, median (min–max) or frequency (%). Mann–Whitney *U* test was used for nonparametric variables among MUC groups and cyst fluid CEA. The compatibility of MUC groups and SS was investigated by Cohen's kappa test. Accepted limit values of Kappa statistics are as follows: $K < 0$ no fit, $0.00 < k < 0.20$ weak, $0.21 < k < 0.40$ mild, $0.41 < k < 0.60$ moderate, $0.61 < k < 0.80$ good, $0.81 < k < 0.92$ very good, excellent fit of $0.93 < k < 1.00$. Statistical significance was considered for $P < .05$.

RESULTS

Clinical Features of the Patients

We evaluated a total of 466 patients with pancreatic cysts via EUS-FNA between 2011 and 2018. Of these patients, 102 (21.8%) were definitively diagnosed as mucinous PCLs cytopathologically. In a retrospective manner, we aimed to investigate the compatibility of positive SS with prespecified MUC expression types (MUC1, MUC2, MUC4, MUC5AC, and MUC6) in 18 mucinous PCL patients with available tissue samples for immunohistochemical evaluation. The clinicopathological features of the patients are summarized in Table 1.

In these patients, we first evaluated the expression of prespecified MUC types. Then we evaluated the compatibility between MUC types and SS test (Table 2).

MUC Expression

Prespecified MUC expression types MUC1, MUC2, MUC4, MUC5AC, and MUC6 were investigated in a total of 18 patients with available cytopathological tissue material. Unfortunately, MUC4 expression could not be evaluated in 10 cases due to lack of tissue material. Table 3 shows MUC expression types in mucinous PCLs.

In our study, we detected MUC1 expression in 10/10 (100%) HR cysts. MUC5AC was expressed in almost all cyst types (88.9%) (Tables 2 and 3).

Figure 1 shows hematoxylin and eosin and immunohistochemical staining of the tissue materials for MUC1 expression obtained via fine needle biopsy cell blocks (A and B) or from the resection materials (C and D).

Table 1. Baseline Demographics of the Available Definitively Diagnosed Mucinous PCL With Tissue Material and Viscosity Assessment

Gender F, (%)	11, (61.1)
Age, mean ± SD	59.7 ± 13.3
Location*	
1. Head-uncinate	10 (55.6)
2. Corpus	5 (27.8)
3. Tail	3 (16.7)
Cyst sizes mm, median (min-max)	
1. LR-MCN	60 (50-65)
2. LR-IPMN	35 (13-60)
3. HR-IPMN	30 (17-45)
4. Cystic PDAC	33 (15-50)
Cyst fluid CEA, *n*, ng/mL, median (min-max)	11, 1159.2 (40.3-53445)
Available tissue material by*	
1. Resection	12 (66.6)
2. Cytologic	6 (33.4)
Final cytopathological diagnosis*	
1. LR-MCN	3 (16.7)
2. LR- IPMN	5 (27.8)
3. HR-IPMN	6 (33.3)
4. Cystic PDAC	4 (22.2)
String Sign Test*	
a. Positive *n*, % (11, 61.1)	1. LR-MCN (3, 100)
	2. LR-IPMN (3, 60)
	3. HR-IPMN (3, 50)
	4. Cystic PDAC (2, 50)
b. Negative *n*, % (7, 39.9)	1. LR-IPMN (2, 40)
	2. HR-IPMN (3, 50)
	3. Cystic PDAC (2, 50)

*Values are *n* (%).
IPMN, intraductal papillary mucinous neoplasia; MCN, mucinous cystic neoplasia; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

Viscosity Assessment SS Test

As shown in Table 1, 11(61.1%) patients had a positive SS test. While SS test was positive in all LR-MCNs, the positivity and negativity of the SS test was equal in LR and HR IPMNs and cystic PDACs.

Compatibility of Positive SS with Prespecified MUC Expression Types and Cyst Fluid CEA in Mucinous PCLs

Table 4 shows the results of Cohen's kappa test between the prespecified MUC expression and SS test. We did

Table 2. MUC Staining and SS Test Results in Mucinous PCLs

Patient	Age, y/Gender	Cyst Type	String Sign Test	MUC1	MUC2	MUC4	MUC5AC	MUC6
1.	36, F	LR-MCN	P	+	+	–	+	+
2.	24, F	LR-MCN	P	–	–	NA	+	+
3.	54, F	LR-MCN	P	–	–	NA	+	+
4.	74, M	LR-IPMN	P	–	+	+	+	–
5.	60, M	LR-IPMN	P	+	+	–	–	+
6.	62, M	LR-IPMN	P	–	–	NA	+	+
7.	55, F	HR-IPMN	P	+	–	–	+	+
8.	72, F	HR-IPMN	P	+	–	NA	+	–
9.	61, M	HR-IPMN	P	+	–	NA	+	–
10.	59, F	Cystic PDAC	P	+	–	+	+	+
11.	75, F	Cystic PDAC	P	+	–	NA	+	–
12.	72, M	LR-IPMN	N	+	–	–	+	+
13.	58, F	LR-IPMN	N	+	–	–	+	+
14.	56, M	HR-IPMN	N	+	–	–	+	-
15.	74, F	HR-IPMN	N	+	–	–	–	–
16.	64, F	HR-IPMN	N	+	–	–	+	+
17.	51, M	Cystic PDAC	N	+	–	NA	+	+
18.	68, F	Cystic PDAC	N	+	–	NA	+	–

F, female; M, male; N, negative; P, positive; PDAC, pancreatic ductal adenocarcinoma.

Table 3. Prespecified MUC Expressions in 18 Mucinous PCL Patients

	LR-MCN ($n = 3$)	LR-IPMN ($n = 5$)	HR-IPMN ($n = 6$)	Cystic PDAC ($n = 4$)
MUC1	1 (33.3%)	3 (60%)	6 (100%)	4 (100%)
MUC2	1 (33.3%)	2 (40%)	0 (0%)	0 (0%)
MUC4*	0 (0%)	1 (20%)	0 (0%)	1 (25%)
MUC5AC	3 (100%)	4 (80%)	5 (83.3%)	4 (100%)
MUC6	3 (100%)	4 (80%)	2 (33.3%)	2 (50%)

*In 10 cases.
HR, high risk; IPMN, intraductal papillary mucinous neoplasm; LR, low risk; MCN, mucinous cystic neoplasia; MUC, mucin; PDAC, pancreatic ductal adenocarcinoma.

not detect a significantly moderate or good agreement among the prespecified MUC expression types (MUC1, MUC2, MUC4, MUC5AC, and MUC6) and the SS test.

We observed mild compatibility between MUC4 expression and the SS test. MUC4 was expressed in 2 of 10 patients who also had a positive SS test. According to histopathologic diagnosis, one of these patients was diagnosed as cystic PDAC and the other was diagnosed as LR-IPMN.

Cyst fluid CEA levels did not differ between those expressing and not expressing prespecified MUC types (all $P < .05$). Also, cyst fluid CEA did not differ between positive and negative SS test-detected cysts ($P = 584$).

DISCUSSION

Currently, detection of high-grade dysplasia or invasive carcinoma in pancreatic mucinous cysts is not sufficient. One of the reliable methods in this regard is the determination of aberrant MUC types that can trigger malignant transformation expressed by mucinous cysts.[11] The role of MUC1, MUC4, and MUC 16 in pancreatic cancer is evident, but there is still insufficient data on other MUC types.[12]

In mucinous cysts, the viscosity of the cyst fluid increases due to MUC in the cyst content. However, to the best of our knowledge, the relationship between the MUC types and high cyst fluid viscosity is unknown. SS test is a practical method of evaluating the viscosity of cyst aspirate

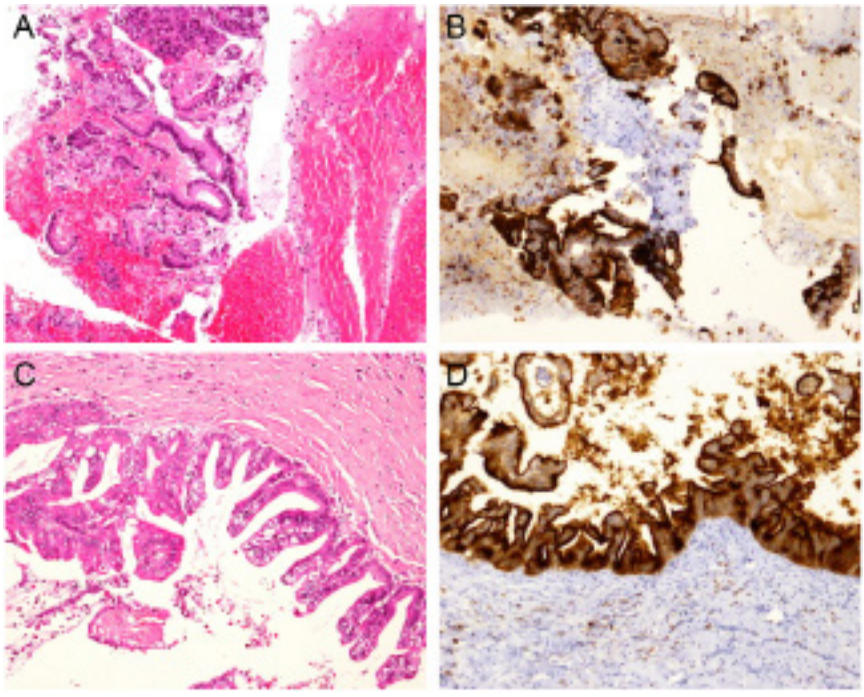

Figure 1. Specimen for immunohistochemical study of cytology with the cell-block method and resection materials. (A) Cell block H&E staining (orig. mag. ×100). (B) Cell block immunohistochemical MUC1 expression (orig. mag. ×100). (C) Resection material H&E staining (orig. mag. ×200). (D) Resection material immunohistochemical MUC1 expression (orig. mag. ×200). MUC, mucin; H&E, hematoxylin and eosin.

Table 4. Prespecified Mucin Expressions (MUC 1, 2, 4, 5AC, and 6) and String Sign Test Results of the 18 Patients With Kappa Coefficient

Prespecified MUC Expression Types		String Sign		
		Negative	Positive	Kappa
MUC1	Negative *n*, %	0	4 (100)	−0.394
	Positive *n*, %	7 (50)	7 (50)	
MUC2	Negative *n*, %	7 (46.6)	8 (53.3)	0.226
	Positive *n*, %	0	3 (100)	
MUC4	Negative *n*, %	5 (62.5)	3 (37.5)	0.400
	Positive *n*, %	0	2 (100)	
MUC5AC	Negative *n*, %	1 (50)	1 (50)	0.060
	Positive *n*, %	6 (37.5)	10 (62.5)	
MUC6	Negative *n*, %	3 (42.8)	4 (57.1)	0.065
	Positive *n*, %	4 (36.3)	7 (63.6)	

MUC, mucin.

and, when combined with the cyst fluid CEA level, it was considered to increase the diagnostic accuracy of mucinous PCLs.[8] Since the evaluation of MUC typing at the diagnostic stage is associated with clinicopathological features, it is thought to be useful in predicting the morphological features of the cyst in the preoperative period.[13]

We hypothesized that in a high viscosity cyst fluid, there may be a certain type of MUC to which viscosity may depend. Thus, when the cyst fluid viscosity is evaluated by SS test, MUC type can be predicted without further tests. For this purpose, we included 18 patients with retrospective cytopathological definitive diagnosis, appropriate tissue material, and prediagnostic SS test. First, we identified prespecified MUC expressions in these patients by immunohistochemical staining. Then we evaluated the consistency between prespecified MUC types and positive SS test.

Accordingly, in this study we found that all HR cysts expressed MUC1 significantly (Table 3) in agreement with previous studies.[14-17] While MUC1 expression was 100% in HR-IPMN and cystic PDAC, it was 60% in LR-IPMN and 33.3% in LR-MCN (Table 3). When we evaluated the compatibility of MUC1 expression and the SS test, the Cohen's kappa value was in the negative range (k = −0.394). Accordingly, we may consider that MUC1 and the SS test were completely incompatible. Therefore, MUC1 expression, which is an established precursor of malignancy, cannot be predicted by the SS test.

Although MUC2 expression was reported to be associated with HR cysts in some studies, in our study MUC2 was positively expressed in 3 patients with LR cysts.[6,12,18] However, MUC2 expression of these cysts was not compatible with the SS test.

In recent years, MUC4 is considered to be one of the poor prognostic indicators in pancreatic adenocarcinomas. There are earlier studies indicating that MUC4 is a tumor-associated MUC and is thought to be involved in the development of IPMN.[19,20] Recent studies considered MUC4 as one of the precursors of malignancy. However, MUC4 expression in IPMN and MCN is unknown.[6] In our study, MUC4 was expressed in 2 of the 10 available patients. One of the cysts in which it was expressed was LR-IPMN and the other was cystic PDAC. SS was positive in both patients with MUC4 expression. We found mild compatibility between positive SS and MUC4 expression ($k = 0.40$) (Table 4).

MUC5AC is expressed in many types of pancreaticobiliary diseases, both benign and malignant.[6] In this study, MUC5AC was expressed in 16 (7 LR, 9 HR cysts) of 18 patients at a similar rate between LR and HR cysts. We found MUC5AC expression between 80 and 100% in LR and HR cysts. However, MUC5AC expression and SS test were not compatible ($k = 0.06$).

MUC6 is not thought to be related to clinical progression.[12] In this study, we found that MUC6 was expressed in 11 (7 LR, 4 HR) patients. MUC6 expressing cyst ratios were as follows: LR-MCNs 100%, LR-IPMNs 80%, HR-IPMNs 33.3%, and cystic PDACs 50%. It was highly expressed in benign cysts (Table 3). However, we found no compatibility between MUC6 expression and SS test.

In addition, we compared cystic fluid CEA levels and the prespecified MUC expressions. We found no significant relationship between cyst fluid CEA levels and prespecified MUC expressions (all $P > .05$). Also, cyst fluid CEA was not different between SS test-positive and -negative cysts.

To the best of our knowledge, this is the first report on the assessment of MUC expression compatibility with positive SS. However, our study has some limitations. The main limitations were the single-center design and the small sample size due to its retrospective nature. Our study was planned retrospectively as it was based on tissue material and was intended to test a hypothesis. Hence, only a small number of patients could be included with available paraffin-embedded archival samples for immunohistochemical staining and SS test results.

In conclusion, we found that MUC1 is expressed in all malignant cysts. However, MUC1 expression was not compatible with the SS test. MUC4, on the other hand, showed mild compatibility with the SS test in a small number of patients.

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Informed Consent: Since it was a retrospective study on the recorded material and pathology specimens.

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