Fine Needle Aspiration Diagnosis of Mucinous Cystic Neoplasms and Intraductal Papillary Mucinous Neoplasms of the Pancreas: Cytomorphology, CEA Level and *KRAS* Mutation Status

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INTRODUCTION

Mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) are the two most common mucinous lesions in the pancreas. Recognition of these mucinous lesions preoperatively is important due to their potential association with variable dysplasia and even invasive carcinoma. Since the patients with invasive MCNs are 5-10 years older than the patient with noninvasive MCNs, suggesting that progression from a noninvasive curable neoplasm to an invasive cancer occurs over a a period of years. Similar findings are also seen in the patients with IPMNs.

With advances in imaging techniques, more and more pancreatic lesions are identified. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) biopsy is becoming the choice of modality for diagnosing and classifying pancreatic lesions. However, accurate diagnosis of pancreatic lesions, especially cystic lesions, could be difficult based on cytomorphologic features alone due to low cellularity and overlapping cytomorphology. Previous studies have demonstrated that carcinoembryonic antigen (CEA) level analysis of cystic fluids could be helpful in differentiating mucinous from non-mucinous cysts. KRAS mutation has been implicated in pathogenesis of pancreatic neoplasms and KRAS mutation testing can improve diagnostic yield in cases with indeterminate cytological diagnoses.

In this retrospective study, we review the results of cytological diagnosis, CEA level and KRAS mutation status in MCNs and IPMNs diagnosed by histopathologic examination.

MATERIALS AND METHODS

The institutional database was search for all cases with a diagnosis of pancreatic lesions by EUS-FNA biopsy with surgical follow-up of either MCNs or IPMNs at Yale-New Haven Hospital between January 2005 and June 2011. A total of 61 cases were retrieved from cytopathology and histopathology archives, of which 25 cases (41%) were MCNs and 36 cases (59%) IPMNs on surgical follow-up. Patient's clinical information including imaging study findings, cytopathologic and surgical pathology diagnoses were retrospectively reviewed.

FNA biopsy was performed under endoscopic ultrasound (EUS) guidance using 25-gauge needles. The aspirates were smeared and air-dried or fixed in 95% of alcohol and stained with Diff-Quik or Papanicolaou techniques. Rapid on-site evaluation was performed in some cases by a cytopathologist to ensure adequate sampling, appropriate specimen triage, and preliminary diagnosis. In cases lacking a significant solid component, the aspirates were saved in Cyto-Rich fixative and processed for a Papanicolaou-stained Thin-Prep slide. Final cytologic diagnoses were rendered based on cytomorphologic analysis alone.

In some cases, part of the aspirates were sent for cyst fluid analysis including CEA level. A CEA level of more than 192 ng/ml was considered as elevated, suggesting a mucinous cyst. In selective cases, KRAS mutation testing was performed on remaining washing specimens or cell block materials using polymerase chain reaction-single strand conformational polymorphism (PCR-SSCP) analysis of KRAS gene exon 2 at the codons 12 and 13.

The clinicopathologic features of MCN and IPMN cases included in this study were analyzed. The corresponding final cytologic diagnoses, cyst fluid CEA level and KRAS mutation status were retrospectively reviewed and correlated with the results of surgical follow-up. The sensitivities of each and combinational tests were calculated and compared.

RESULTS

1. Clinicopathologic Features (Table 1)

The patients were 21 males and 40 females with ages raging from 27 to 82 years old. The pancreatic lesions included 25 MCNs with low, intermediate and high grade dysplasia in 21, 1, and 3 cases, respectively and 36 IPMNs with low, intermediate, and high grade dysplasia in 17, 10, and 9 cases, respectively. The majority of the lesions (59%) were located in the head, neck or uncinate of the pancreas. Other locations included the body (15%) and tail (26%). The lesions ranged from 0.4 to 12 cm, with a mean of 3.6 cm.

2. Cytological Diagnoses (Table 2)

For the cases of MCNs, the cytological diagnoses of negative, suspicious or positive for mucinous neoplasm, and adenocarcinoma were rendered in 14 (56%), 8 (32%) and 3 (12%) cases. For the cases of IPMNs, the cytological diagnoses of negative, suspicious or positive for mucinous neoplasm, and adenocarcinoma were rendered in 10 (28%), 20 (56%) and 6 (17%) cases.

3. CEA Level and KRAS Mutation Status (Table 2)

Cyst fluid analysis of CEA was performed in 14 of 25 (56%) MCNs and 7 of 36 (19%) IPMNs. Using the cutoff of 192 ng/ml, CEA level was elevated in 11 of 14 (79%) tested MCNs and 6 of 7 (86%) tested IPMNs. KRAS mutation analysis was performed in 13 of 25 (52%) MCNs and 15 of 36 (42%) IPMNs. KRAS mutation was identified in 7 of 13 (54%) tested MCNs and 8 of 15 (53%) tested IPMNs.

4. Sensitivities of Cytomorphology, CEA Level and KRAS Mutation Analysis

Based on cytomorphologic features, mucinous neoplasm was recognized in 11 of 25 MCN cases (44%) and in 26 of 36 IPMN cases (72%) including a malignant diagnosis in 3 MCNs and 6 IPMNs. By combining cytomorphologic features with CEA level and KRAS, the sensitivity for identification of mucinous neoplasm was increased from 44% to 68% in MCNs and from 72% to 83% in IPMN cases.

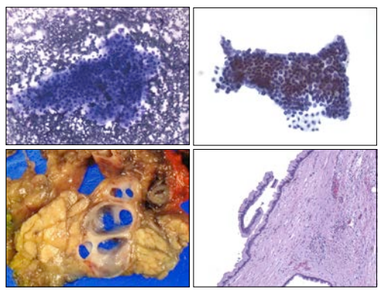

Figure 1. Cytomorphologic and histopathologic features of mucinous cystic neoplasm.

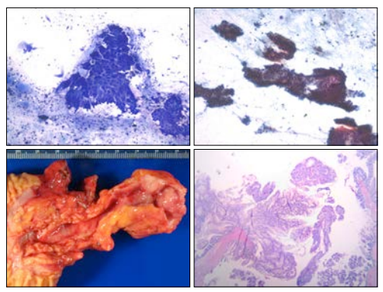

Figure 2. Cytomorphologic and histopathologic features of intraductal papillary mucinous neoplasm.

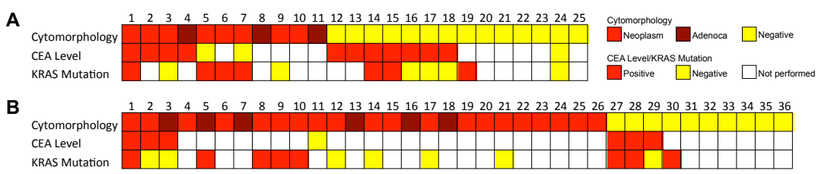

Figure 3. Cytomorphology, CEA level and KRAS mutation status of mucinous cystic neoplasm (A) and intraductal papillary mucinous neoplasm (B).

Table 1. Clinicopathologic Features of Mucinous Cystic Neoplasm and Intraductal Papillary Mucinous Neoplasm

	Mucinous Cystic Neoplasm		Intraductal Papillary Mucinous Neoplasm	
Patient Age (year)				
Range	27~76		40~82	
Mean	51		66	
Patient Gender				
Male	4	16%	17	47%
Female	21	84%	19	53%
Location of the Lesion				
Head/Neck/Uncinate	8	32%	28	78%
Body	3	12%	6	17%
Tail	14	66%	2	6%
Size of the Lesion (cm)				
Range	1.3~12		0.4~10	
Mean	4.2		3.2	
Surgical Diagnosis				
Low Grade Dysplasia	21	84%	17	47%
Intermediate Dysplasia	1	4%	10	28%
High Grade Dysplasia/Adenocarcinoma	3	12%	9	25%

Table 2. Cytological Diagnosis, CEA Level and KRAS Mutation Status of Mucinous Cystic Neoplasm and Intraductal Papillary Mucinous Neoplasm

	Cytological Diagnosis			CEA Level		KRAS Mutation	
	Negative	Neoplasm	Malignant	< 192 ng/ml	>= 192 ng/ml	Negative	Positive
Mucinous Cystic Neoplasm	14	8	3	3	11	6	7
Low Grade Dysplasia	14	7	0	3	9	6	6
Intermediate Dysplasia	0	1	0	0	1	0	1
High Grade Dysplasia/Adenocarcinoma	0	0	3	0	1	0	0
Intraductal Papillary Mucinous Neoplasm	10	20	6	1	6	7	8
Low Grade Dysplasia	7	10	0	1	5	4	4
Intermediate Dysplasia	3	7	0	0	0	1	3
High Grade Dysplasia/Adenocarcinoma	0	3	6	0	1	2	1

CONCLUSIONS

- Mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasms (IPMN) have distinct clinicopathologic characteristics and are associated with variable degree of dysplasia.
- EUS-FNA has a higher sensitivity for identifying IPMNs than MCNs based on the analysis of cytomorphologic features alone.
- CEA level and KRAS mutation analysis increase the sensitivity of EUS-FNA, especially for MCNs, and should be incorporated into the final diagnosis of EUS-FNA.

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