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ORIGINAL ARTICLE

Endoscopic Ultrasound-Guided Fine-Needle Aspiration Cytology in the Diagnosis of Intraductal Papillary Mucinous Neoplasms of the Pancreas. A Study of 8 Cases

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ABSTRACT

Context Intraductal papillary mucinous neoplasm (IPMN) is an increasingly recognized neoplasm of the pancreas, accounting for 5% of pancreatic neoplasms, it is considered difficult to diagnose by fine-needle aspiration (FNA) cytology.

Objective The aim of this study was to investigate the role of EUS-guided FNA cytology in the diagnosis of IPMN of the pancreas.

Patients Eight cases of surgically proven IPMN with pre-operative endoscopic ultrasound-guided (EUS-guided) FNA cytology were collected for retrospective analysis.

Main outcome measures EUS-FNA cytology was performed with the on-site attendance of a cytopathologist in all cases. EUS/clinical findings, macroscopic/micro-scopic features of cell blocks and smears, and immunocytochemical stains accompanied by histopathologic diagnosis were recorded and studied.

Results EUS revealed hypoechoic masses in the head of pancreas (n=6) and in the body/tail (n=2), measuring from 16.6 to 35.8 mm. In all cases, the hypoechoic mass had a distinctive distribution, involving the main pancreatic duct and/or the associated large branch ducts while intraductal nodules or multiple cysts were detected. Cytological specimens were characterized by a background containing abundant mucin in all cases and rarely by inflammation (neutrophils and histiocytes) (n=4). Neoplastic cells were entrapped in a mucinous background either single or loosely cohesive, and forming papillae in 7 cases. Mucinous epithelium was observed in all cases. Single atypical and irregular clusters were found in 3 cases (which were cytologically described as highly suggestive malignant IPMNs, and were histologically confirmed). Two cases were diagnosed as benign IPMN and, in 3 cases, the biological behavior was not easy to determine by cytology alone (histologically diagnosed as borderline). The histological diagnosis confirmed the FNA cytology diagnosis: 3 malignant IPMNs, 2 benign IPMNs and 3 borderline IPMNs. Immuno-stains were available in 5 out of 8 cases. Mucin 1 (MUC-1) was positive in 2 cases of malignant IPMN (histologically classified as null type ad intestinal type), mucin 2 (MUC-2) was positive in 3 cases (2 malignant both of the intestinal type, and 1 benign of the intestinal type I) and c-erbB2 was positive in 3 cases (2 benign - null and intestinal type - and 1 malignant null type).

Conclusions The characteristic pre-operative EUS findings and cytomorphologic features, in addition to the immunocytochemical profile, were accurate indications and coincided with the final/post-operative histological diagnosis of IPMN.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) (also known as intraductal papillary mucinous tumor: IPMT) is an increasingly recognized mucin-producing cystic neoplasm of the pancreas, first distinguished from mucinous cystic neoplasm and ductal-adenocarcinoma in 1982 [1]. These neoplasms account for approximately 5% of pancreatic neoplasms [2] although this figure may, in fact, be an underestimation because the terminology has not yet been standardized [3]. The term "IPMN" is applied to a spectrum of proliferate epithelial lesions ranging from hyperplasia to adenocarcinoma "in-situ". Macroscopically, IPMN is characterized by the mucinous dilation of the pancreatic ducts, with involvement of either the main duct alone (main duct type), side branch ducts (side branch type), or both (combined type). These neoplasms are histologically classified based on architectural complexity and the severity of epithelial atypia into IPMN-adenoma, IPMN with moderate dysplasia, or IPMN with carcinoma, either in situ or invasive (tubular type or colloid carcinoma) [4]. Compared to conventional ductal adenocarcinoma, IPMN with invasive carcinoma has a better prognosis [5] and, for IPMNs, the presence or absence of an invasive carcinoma is the most important prognostic factor for survival.

Modern imaging techniques including EUS, computerized tomography (CT), and magnetic resonance imaging (MRI) are sensitive tests for the detection of IPMNs. These studies visualize dilated and cystic pancreatic ducts. Endoscopic retrograde cholangiopancreatography (ERCP) is highly successful at demonstrating the nature of the lesion and establishing the presence of copious intraductal mucus. This technique allows cytological sampling of the lesion. Recently, computer-aided three-dimensional reconstructions of the pancreatic duct system have subdivided IPMNs into four subtypes as described by Furukawa *et al*. [6]. EUS-FNA cytology is an excellent method for procurement of diagnostic samples from the pancreas, with a diagnostic accuracy of more than 90% for pancreatic adenocarcinoma [7]. EUS-FNA is currently used for the pre-operative diagnosis of pancreatic cysts and for small neoplasms, but the introduction of gastric or duodenal epithelium and mucin into the specimen during the procedure (e.g. gastrointestinal contamination) has created diagnostic challenges, particularly in the area of mucinous cysts of the pancreas [8]. EUS-FNA allows placement of the needle inside the dilated ductal system, at several levels if necessary in order to distinguish IPMNs from other causes of duct dilation such as obstruction or chronic pancreatitis. Although there are several reports in the literature on EUS diagnosis of IPMN [9, 10, 11, 12], to our knowledge, the utility of EUS-FNA cytology has not been well-established [13, 14].

The aim of this study was to investigate the role of EUS-guided FNA cytology in the diagnosis of IPMNs of the pancreas. We explored the combination of the available cytological features and the immuno-cytochemical profile in determining the biological behavior of these tumors. Moreover, these findings were compared to the final histological examination.

MATERIALS AND METHODS

A search of the laboratory information system at the Department of Cytology in Athens General Hospital identified 8 patients between January 2005 and May 2007 with cytologically proven IPMNs. All cases were accompanied by a final pathologic diagnosis and surgical resection. The histologic diagnosis was compared to the cytologic diagnosis. In each case, the cytological and histological slides were pulled for review. EUS-guided FNA was performed in all cases using 22-gauge needles via a transgastric approach, with the on-site attendance of a

cytopathologist in all cases. The aspirated material was smeared onto glass slides, air-dried, and immediately stained with rapid hemo-color stain for specimen adequacy assessment and preliminary diagnostic interpretation. Other smears were also fixed immediately in 95% alcohol for subsequent Papanicolaou staining. Additional aspirated material was fixed in formalin, embedded in paraffin, and processed for routine histologic examination using standard techniques. All surgical specimens were 10% neutral buffered formalin-fixed with representative portions being prepared as paraffin blocks from which 5-micron hematoxylin and eosin (H&E) stained sections were prepared. The surgical pathology material was reviewed to confirm the nature of the lesion, establish the grade of the neoplasm and determine if invasive carcinoma was present.

The cytological smears were divided into three groups according to specimen cellularity: low, moderate and marked. Each specimen was categorized into one of these groups based on the epithelium content percentage of each slide. Specimens graded as low cellularity had less than 10% of the specimen area of the glass covered with epithelium, those with 10-40% of the specimen covered with epithelium were graded as moderate cellularity and those with more than 40% of the specimen covered with epithelium were graded as high cellularity. The following features were assessed for each cytologic smear: the nature and amount of extracellular mucin, cellularity and distribution of neoplastic cells, the presence or absence of papillary fragments, nuclear crowding, nuclear molding, the presence of goblet cells, presence of intracellular-mucin, the presence of nuclear membrane irregularities, the presence of macronucleoli, and inflammatory debris/necrosis. We also evaluated the presence or absence of vacuolated cytoplasm, mitoses, parachromatin clearing and nuclear grooves.

The cytologic characteristics of individual specimens were compared with one another based on the histologic grade of the resected IPMN.

Also, as regards papillary patterns on histological examination, IPMNs were classified into three groups: 1) those that were composed of long finger-like projections and lined by columnar cells were classified as intestinal type; 2) IPMNs composed of complex arborizing papillae lined by cuboidal cells were classified as pancreatobiliary type; and 3) IPMNs lined by tall columnar cells with abundant pale supranuclear mucin, reminiscent of gastric foveolar cells were classified as null type (gastric foveolar type).

Furthermore, immunocytochemical stains were carried out by using the following antibodies: mouse monoclonal anti-mucin-1 antibody (clone Ma695) (Novocastra Laboratories, Newcastle, UK), anti-mucin-2 antibody (clone Ccp58) (Novocastra Laboratories, Newcastle, UK) and polyclonal anti-c-erbB2 antibody (Dako, Glostrup, Denmark). The immunostains were available for 5 cases. The avidin-biotin peroxidase complex technique was used.

ETHICS

The study protocol conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 (as revised in Tokyo 2004) as reflected in the approval by the “Department of Cytology, Athens General Hospital, Greece” review committee. No informed consent was obtained because the studies were carried out during routine clinical examinations.

STATISTICS

Descriptive statistics are reported.

RESULTS

Clinical-EUS Findings

The main clinicopathological features and the original cytologic diagnosis are shown in Table 1. Five patients were male and 3 were female, with a median age of 66.8 years and 57.3 years respectively (range: 46-75 years). Of the 8 neoplasms, 6 were present in the head of the pancreas (75.0%) and 2 were

Table 1. Clinical features, and original cytological and histological diagnosis.

Case No.	Age (years)	Gender	Location	Diagnosis	
				Cytology	Histology
1	59	Male	Head	IPMN	IPMN borderline - PBT
2	58	Female	Body/tail	IPMN suspicious as malignant	IPMN malignant-invasive - NT
3	68	Female	Head	IPMN	IPMN borderline - NT
4	51	Male	Head	IPMN	IPMN borderline - PBT
5	46	Female	Head	IPMN benign	IPMN benign - NT
6	74	Male	Head	IPMN suspicious as malignant	IPMN malignant-invasive - IT
7	75	Male	Body	IPMN benign	IPMN benign - IT
8	75	Male	Head	IPMN suspicious as malignant	IPMN malignant IT

PBT: pancreatobiliary type
NT: null type
IT: intestinal type

identified in the body/tail region. EUS revealed multiple (n=4) or simple (n=4) cystically dilated hypoechoic masses, measuring from 16.6 to 35.8 mm. (Figure 1ab). Four of these neoplasms contained hypoechoic material inside, suspicious of mucus. All lesions communicated with a distally dilated main pancreatic duct. The EUS report was highly suggestive of IPMN in 6 cases (75.0%) and the proposed differential diagnosis of mucinous cystadenoma and IPMN was made for the other 2 cases (25.0%).

Cytologic Features

Three specimens were labeled as low cellularity, 3 as moderate and 2 as high cellularity. The findings from the cytologic analysis are shown in Table 2. The quantity and thickness of the mucin varied. Mucin was evident on macroscopic examination at the time of aspiration in all cases. In 3 cases, the mucin was admixed with blood in the background. The mucin was thick, viscous and occasionally "colloid-like". Inflammatory cells mainly of histocytoid type were observed in 2 cases and other inflammatory cells (neutrophils and/or lymphocytes) in 2 cases.

Epithelial cells were entrapped in a mucinous background and were arranged in papillae (n=7) and in loosely cohesive sheaths (Figure 2abc). Papillae were accompanied by fibrovascular cores. Micropapillary clusters were seen in malignant cases. Similarly, irregular clustering and discohesiveness with

Table 2. Cytomorphological features.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Quantity of mucus	+++	+++	+++	+++	+++	+++	+++	+++
Cellularity	+	+++	+	+	++	++	++	+++
Sheets	-	+	-	-	-	+	-	+
Papillae	+	+	+	+	+	+	+	-
Irregular clusters	-	+	-	-	-	+	-	+
Single atypical cells	-	+	-	-	-	+	-	+
Mucinous cells	+	+	+	+	+	+	+	+
Nuclear atypia	-	+	-	-	-	+	-	+
Inflammation	+	+	-	-	-	+	-	+
Nuclear/cytoplasmic ratio	High	High	High	High	Normal	High	Normal	High

single atypical cells were features of borderline and highly suspicious malignant lesions. Mucinous type epithelium was observed in all cases. Also, neuroendocrine-type epithelium was found in 1 case. In 3 cases with malignant IPMN, the neoplastic cells had atypical features: nucleolus, nuclear overlapping, atypical polarization, prominent mitoses and nuclear grooves. Prominent nucleoli, nuclear overlapping and mitoses were absent from the benign IPMNs. Cellular atypia correlated with the final histopathologic diagnosis. In all cases, the cytologic diagnosis coincided with the final histologic diagnosis (100%).

Moreover, histologically, 3 out of the 8 cases had papillae of the intestinal type (2 malignant and 1 benign) (cases No. 6, 7, and 8 in Table 1), 3 cases were of the null type (1 malignant, 1 borderline, and 1 benign) (cases No. 2, 3, and 5 in Table 1), and 2 cases were of the pancreatobiliary type (2 borderline) (cases No. 1 and 4 in Table 1).

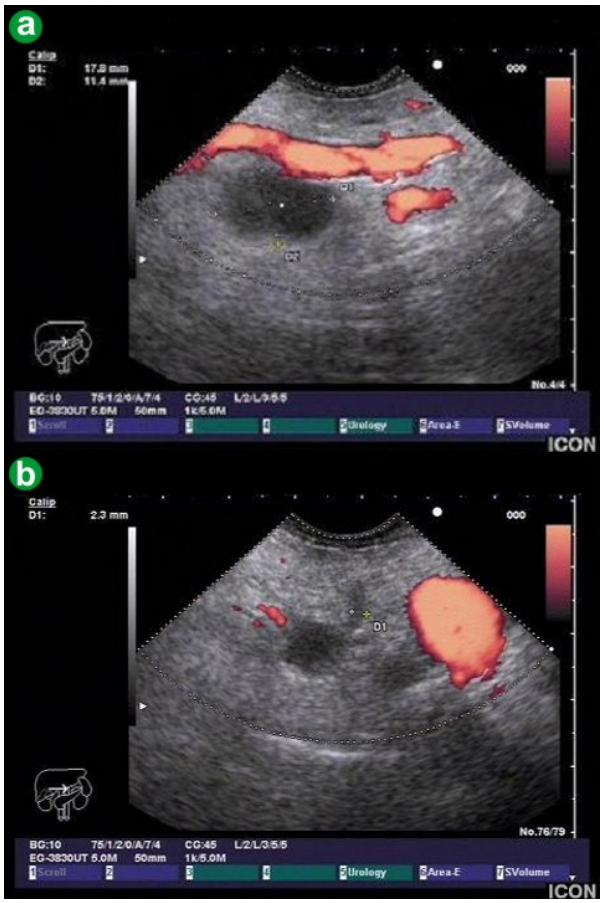

Figure 1. EUS finding revealing a hypoechoic mass in the head of the pancreas, communicating with the main pancreatic duct.

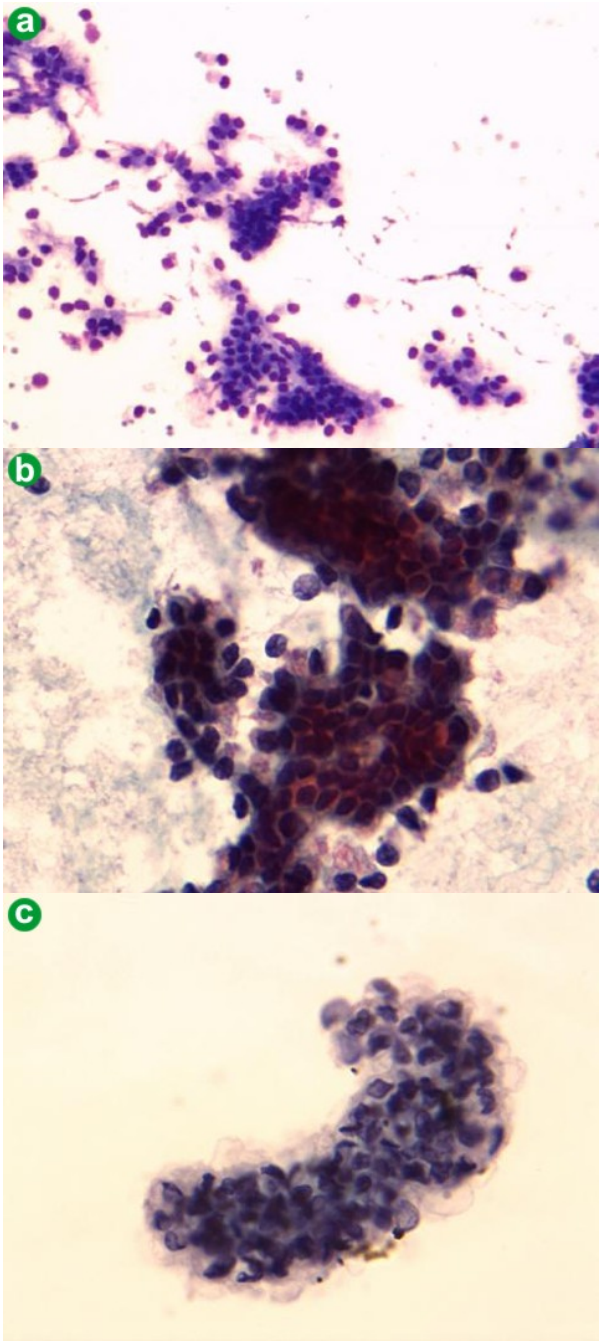

Figure 2. a. Mucus cells in a smear (x100). **b.** Mucus cells in a mucin background (x400). **c.** Well-formed papilla (x400).

Immunohistochemistry was performed for 5 cytologic specimens due to limited cellularity in the other 3 specimens (cases 1, 3, and 4 in Table 1). Mucin-1 (MUC-1) was positive in 2 cases with a cytological diagnosis of malignant IPMN (null and intestinal type) and negative in 3 cases (Figure 3a). Mucin-2 (MUC-2) was positive in 3 cases: 2 cases with the cytological features of malignant IPMNs and 1 case of benign IPMN (all cases were of

the intestinal type) (Figure 3b). c-erbB2 was positive in 3 cases: 2 cases with benign IPMNs (null and intestinal type) and 1 case with malignant IPMN (null type) (Figure 3c).

DISCUSSION

Intraductal papillary mucinous neoplasms are cystic neoplasms of the pancreatic ductal system. These neoplasms are histologically classified, based on the degree of epithelial and architectural atypia of the cyst lining, into adenomas, neoplasms with moderate dysplasia, carcinoma in situ and IPMNs with invasive carcinoma. Although their behavior is variable, the prognosis is favorable even when carcinoma in situ is present. Thus, the distinction of IPMNs from other cystic mucinous neoplasms of the pancreas is important. Surgical resection is generally indicated for IPMNs [15, 16, 17] although some authors have stated that branch duct-type lesions [18, 19] and lesions occurring in elderly patients [19] may be exceptions because of their indolent behavior. IPMN has characteristic EUS findings and a histopathological appearance, but definitive cytological criteria for the distinction of IPMNs from cystic mucinous neoplasms and cystic adenocarcinomas have not been well-defined. In this study, we explored the EUS-guided FNA cytological features of 8 cases, with the aim of diagnosing IPMNs with greater accuracy.

The cytologic findings of IPMNs have previously been described [10, 11, 12, 13, 14, 20]. A smear background containing abundant mucin and scattered clusters of cuboidal or columnar cells frequently resulted in the cytological diagnosis of IPMN or was suspicious for IPMN, 'but follow-up revealed a mucinous cystadenoma in certain cases, whereas, in other cases, it revealed a cystic mucinous neoplasm not better classified. These false positive cytological diagnoses of papillary mucinous tumor invariably lacked papillary tissue fragments, gland-like structures, nuclear overlapping, high cellularity or significant nuclear atypia. Background mucin alone did not appear to be predictive of the diagnosis of IPMN and did not distinguish it from other neoplasms and reactive changes. The presence of intracellular mucin was closely correlated to the diagnosis of IPMN. The amount and quality of mucin are also crucial for the identification of this entity [21]. Some have advocated the use of special stains to identify mucin objectively [22, 23]. In our study, thick mucin was easy to demonstrate on

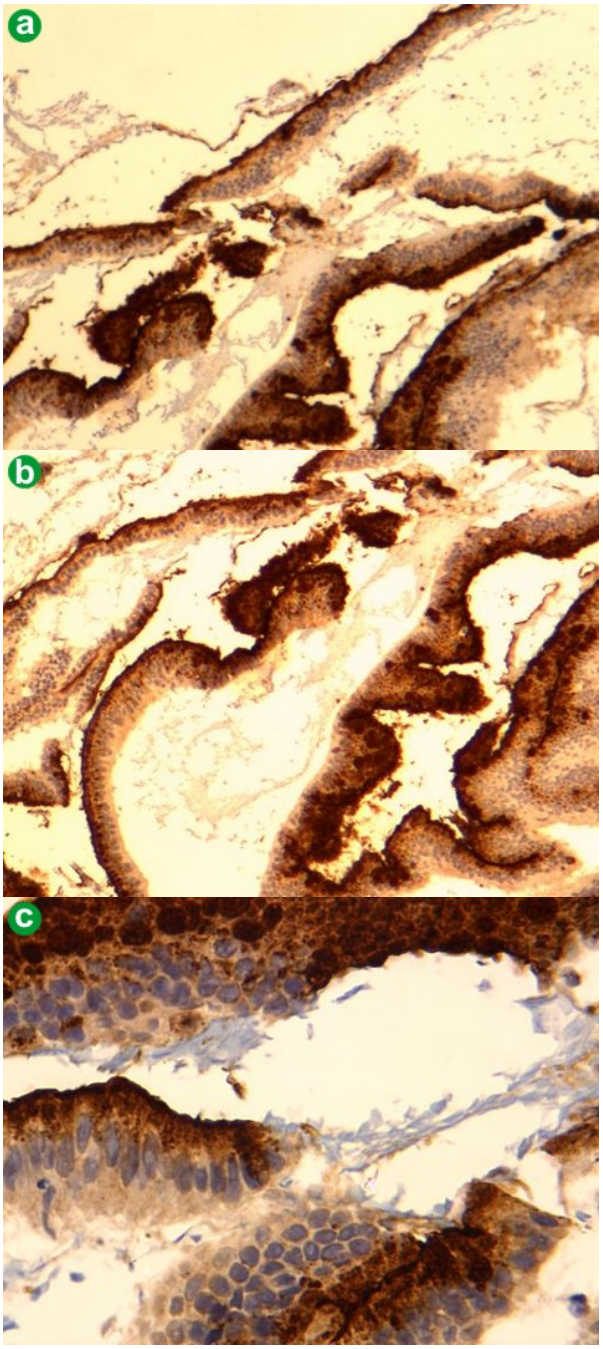

Figure 3. a. Immunostain for MUC-1 in the cytoplasm of cells (x100). **b.** Immunostain for MUC-2 in the cytoplasm of cells (x100). **c.** Immunostain for c-erbB2 (x400).

microscopic examination with routine stains. Furthermore, in all cases, a cytopathologist was always present in the exploration room during the procedure for macroscopic examination of the mucin. The most helpful finding in our study was the presence of many mucinous cells in all cases which was strongly supportive of the diagnosis of IPMN. Loss of mucin production is a sign of dedifferentiation and probably accounts for the presence of non-mucinous epithelium in borderline and malignant cases.

Stelow *et al*. [11] described the EUS and FNA findings in a series of 18 patients with IPMNs and then contrasted the mucinous types between typical IPMNs and the normal epithelial-lined cells of the gastrointestinal tract. Frequently, EUS-guided aspirates are contaminated by epithelial cells scraped from the small intestine and the stomach, and may represent a feature complicating the diagnosis of IPMN. In classic examples of IPMN, the endoscopist can readily identify the abnormal mucin [11] on ultrasound. Stelow *et al*. believed that the abnormal mucin in IPMN significantly differed from that found in normal gastrointestinal tract cells. The normal mucosal epithelium was represented by large flat sheets of duodenal mucosa composed of relatively darker-staining uniform cells. Frequently, these cells have a “honeycomb” pattern interrupted at regular intervals by round, clear goblet cells. In general, the mucus obtained from IPMNs is thicker and more gelatinous than the watery mucin associated with a normal duodenal epithelium. In addition, fewer cells are entrapped in the mucin associated with normal duodenal epithelium than those found enmeshed in the thick gelatinous mucin of IPMNs. IPMN smears lack the “honeycomb” pattern characteristic of normal duodenal epithelium.

Other frequently encountered cytologic features are true papillae with fibrovascular cores, nuclear crowding, nuclear variability, chromatin abnormalities, hyperchromasia, prominent nucleoli and monolayered sheets. A necroinflammatory background is observed only in malignant IPMNs. True papillae with fibrovascular cores were observed in 7 out of 8 cases in our study. We strongly believe that the easily recognized papillae and the mucinous cells in cytologic smears with thick mucinous background are very helpful features in diagnosing IPMNs. The presence of nuclear atypia, nuclear molding, prominent nucleoli, nuclear irregularity and cell crowding appeared to correlate more with the grade of dysplasia present within the lesion rather than the actual type of neoplasm present. Thus, examples of IPMNs with either borderline features or in situ/invasive carcinoma demonstrate these features, but so do mucinous cystadenoma and even pancreatitis with reactive atypia in dilated pancreatic ducts. Hence, these features did not appear to be of diagnostic use in separating IPMNs from other EUS cystic lesions. Michaels *et al*. [14] observed an association only between papillary fragments and IPMN carcinomas. Papillary fragments appeared as a manifestation of the marked architectural complexity seen in IPMN-carcinoma. Therefore, it is not surprising that papillary fragments are more likely to be found in those neoplasms which characteristically have the highest degree of cell proliferation and papillae in the folds. Similarly, irregular or tight epithelial clusters are seen in IPMNs with at least moderate dysplasia. These clusters represent the cellular projections or papillary buds which are often histologically found at the tips of the papillae and tufted along the lining of IPMN cysts with at least moderate dysplasia. We observed these clusters in 3 cases with IPMN carcinomas. Therefore, as a practical issue, the identification of irregular clusters should alert one to the presence of at least moderate dysplasia.

According to several authors with rich experience [10, 11], cytology alone cannot differentiate IPMNs from mucinous cystic neoplasms or ductal adenocarcinomas with a large mucinous component. In most cases, clinical features and imaging studies can distinguish between these lesions. IPMNs are more common in males of advancecd age. In our study, 5 patients were male with a median

age of 66.8 years and 3 were female with a median age of 57.3 years. Mucinous cystic tumors of the pancreas are seen in a younger age group; they predominate in women and have a characteristic ovarian-type stroma in histological sections. Also, they usually occur more distally in the pancreas than do IPMNs [24]. In EUS imaging, six patients appeared with masses in the head of the pancreas and 2 in the body/tail. Ductal adenocarcinomas of the pancreas generally present as solid masses and some may show prominent cystic change [25]. Although the carcinoma does not exhibit communication with the ductal system, it may compress the pancreatic ducts leading to substantial secondary dilation. In some cases, nuclear atypia of IPMNs is similar to that found in ductal adenocarcinomas. Given these issues, some ductal adenocarcinomas may not be able to be distinguished from IPMNs cytologically.

The EUS-FNA technique in diagnosing IPMNs has been recognized of great importance in recent years. The EUS diagnostic findings are: a) solid lesions; b) multicystic lesions, which communicate with a dilated main pancreatic duct; c) ductal filling defects; and d) cysts, which contain hypoechoic material inside suspicious mucus. Cytologic material obtained by EUS-guided FNA has been reported to be highly sensitive in diagnosing IPMN with an overall sensitivity of 68-91% [9, 26, 27]. Our EUS findings revealed multiple or simple hypoechoic masses cystically dilated in the head of the pancreas (n=6) and body/tail (n=2), all of them communicating with the main pancreatic duct. These findings are highly suggestive of a diagnosis of IPMN. Hence, the precise diagnostic sensitivity of EUS-guided FNA cytology findings in our series of 8 cases appears to be very high. This sensitivity was confirmed by the correlation of cytological and histological diagnoses. Five cases correlated cytologically and histologically, and 3 cases of cytologically undetermined biological behavior were classified as borderline lesions in the histopathology report. On the contrary, authors of some studies [10, 11] believe that cytology alone is unable to accurately distinguish IPMNs from cystic mucinous neoplasms, some predominantly cystic adenocarcinomas in the pancreas and rare examples of pancreatitis with extensive cystic change of the pancreatic duct system. However, according to the findings in our study, we believe that IPMNs should be associated with a characteristic endo-sonographic appearance which greatly aids the cytological interpretation of the material obtained from these neoplasms.

An immunohistochemical profile of IPMNs has been well-studied in recent years for the purpose of formulating a prognosis. Increased cytoplasmic expression of caspase-3 is seen in IPMNs with invasive adenocarcinoma [28]. The absence of *p53* overexpression has been associated with a better prognosis and lower grade carcinoma [29, 30]. Three main patterns of staining with CDX2, MUC-2 and MUC-1 immunohistochemical stains have been described in IPMNs [31].

Recent analysis of MUC expression profiles in IPMNs has shown different patterns in histologically distinct types of IPMN [31, 32]. MUCs are a heterogeneous family of glycoproteins, some of which are located in the cell membrane, and others are prepared as secretory products and excreted. MUC-1 has been found to be a marker of an aggressive phenotype, expressed in some higher grade PanINs and, more importantly, presents uniformly in infiltrating conventional ductal adenocarcinoma. MUC-2, on the other hand, is a secretory type mucin which is normally produced almost exclusively in goblet cells. In the pancreas, MUC-2 appears to be a marker of an indolent phenotype in the neoplasms of this organ; it is not expressed in the normal pancreas, PanINs or ductal adenocarcinoma, but it is often detected in IPMNs, especially in the intestinal type.

In our study, MUC-1 was positive in 2 cases of malignant IPMN (null and intestinal type) which seems to correlate with the biological behavior of these tumors. MUC-2 was positive in 3 cases of intestinal type IPMNs (2 malignant and 1 benign) which confirms the close relationship of MUC-2 expression with

intestinal type IPMN, and additionally highlights the possible role of the "intestinal" pathway of carcinogenesis in the pancreas.
Overexpression of the HER2/neu (c-erbB2) product is also a frequent finding, in contrast to its rare expression in ordinary ductal adenocarcinoma [33]. c-erbB2 was positive in 2 cases of benign IPMNs and in 1 case of a malignant IPMN, a fact which emphasizes the possible role of c-erbB2 in the pathogenesis of IPMNs; however, this marker requires further investigation and study.
In conclusion, we believe that close cooperation between an experienced endoscopist and cytopathologist may result in an accurate diagnosis of IPMN, based on EUS-guided FNA cytology. Our study showed that EUS-guided FNA cytology emerges as a valuable and accurate method in the pre-operative diagnosis of IPMNs; EUS-FNA coupled with immunocytochemistry plays a vital role in determining the biological behavior of these tumors.

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References

1. Ohashi K, Murakami Y, Maruyama M. Four cases of "mucin producing" cancer of the pancreas on specific findings of the papilla of Vater. Prog Dig Endosc 1982; 20:348-51.

2. Klimstra DS, Adsay NV. Benign and malignant tumors of the pancreas. In: Odze RD, Goldblum JR, Crawford JM, Eds. Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas. Philadelphia, PA, USA: Saunders, 2004:699-736.

3. Hamilton SR, Aatlonen LA. World Health Organisation Classification of Tumors. Pathology and Genetics of Tumors of the Digestive System. Lyon, France: IARC Press, 2000. [ISBN 92-832-2410-8]

4. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 2004; 28:977-87. [PMID 15252303]

5. Maire F, Hammel P, Terris B, Olschwang S, O'Toole D, Sauvanet A, et al. Intraductal papillary and mucinous pancreatic tumor: a new extracolonic tumor in familial adenomatous polyposis. Gut 2002; 51:446-9. [PMID 12171972]

6. Furukawa T, Takahaski T, Kobari M, Matsumo S. The mucus-hypersecretory tumor of the pancreas. Development and extrension visualized by three-dimensional computerized mapping. Cancer 1992; 70:1505-13. [PMID 1516002]

7. Jhala NC, Jhala DN, Chhieng DC, Eloubeidi MA, Eltoum IA. Endoscopic ultrasound-guided fine-needle aspiration. A cytopathologist's perspective. Am J Clin Pathol 2003; 120:351-67. [PMID 14502798]

8. Stelow EB, Barbales RH, Stanley MW. Pitfall in endoscopic ultrasound-guided fine-needle aspiration and how to avoid them. Adv Anat Pathol 2005; 12:62-73. [PMID 15731574]

9. Maire F, Couvelard A, Hammel P, Ponsot P, Palazzo L, Aubert A, et al. Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. Gastrointest Endosc 2003; 58:701-6. [PMID 14595305]

10. Layfield LJ, Cramer H. Fine-needle aspiration cytology of intraductal papillary-mucinous tumors: a retrospective analysis. Diagn Cytopathol 2005; 32:16-20. [PMID 15584051]

11. Stelow EB, Stanley MW, Barbales RH, Malery S, Lai R, Linzie BM, Pambuccian SE. Intraductal papillary-mucinous neoplasm of the pancreas. The findings and limitations of cytologic samples obtained by endoscopic-ultrasound-guided fine needle aspiration. Am J Clin Pathol 2003; 120:398-404. [PMID 14502804]

12. Shimizu M, Hirokawa M, Manabe T, Mikami Y, Kanahara T, Miyake Y, et al. Cytologic findings in non invasive intraductal papillary-mucinous carcinoma of the pancreas: a report of two cases. Acta Cytol 1999; 43:243-6. [PMID 10097718]

13. Sole M, Iglesias G, Fernandez-Esparrach G, Colomo L, Pellise M, Gines A. Fine-needle aspiration cytology of intraductal papillary mucinous tumors of the pancreas. Cancer 2005; 105:298-303. [PMID 16015637]

14. Michaels PJ, Brachtel EF, Bounds BC, Brugge WR, Pitman MB. Intraductal papillary mucinous neoplasm of the pancreas: cytologic features predict histologic grade. Cancer 2006; 108:163-73. [PMID 16550572]

15. Siech M, Tripp K, Schmidt-Rohlfing B, Mattfeldt T, Gorich J, Beger H. Intraductal papillary mucinous tumors of the pancreas. Am J Surg 1999;177:117-20. [PMID 10204552]

16. Sugiyama M, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: Imaging studies and treatment strategies. Ann Surg 1999; 228:685-91. [PMID 9833807]

17. Traverso L. Surgical treatment of intraductal papillary mucinous neoplasms of the pancreas: the aggressive approach. J Gastrointest Surg 2002; 6:662-3. [PMID 12399053]

18. Seki M. Yanagisawa A, Ohta H, Ninomiya Y, Sakamoto Y, Yamamoto J, et al. Surgical treatment of intraductal papillary-mucinous tumor of the pancreas: Operative indications based on surgico-pathologic study focusing on invasive carcinoma derived from IPMT. J Hepatobiliary Pancreat Surg 2003; 10:147-55. [PMID 14505148]

19. Fernandez-Del Castillo C. Surgical treatment of intraductal papillary mucinous neoplasms of the pancreas: the conservative approach. J Gastrointest Surg 2002; 6:660-1. [PMID 12399052]

20. Recine M, Kaw M, Evans D, Krishnamurthy S. Fine-needle aspiration cytology of mucinous tumors of the pancreas. Cancer 2004; 102:92-9. [PMID 15098253]

21. Centeno BA. Role of cytology in the diagnosis of cystic and intraductal papillary mucinous neoplasms. Gastrointest Endosc Clin N Am 2002; 12:697-708. [PMID 12607780]

22. Frossard JL, Amonyal P, Amonyal G, Palazzo L, Amaris J, Soldan M, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. Am J Gastroenterol 2003; 98:1516-24. [PMID 12873573]

23. Centeno BA, Warshaw AL, Mayo-Smith W, Southern JF, Lewandrowski K. Cytologic diagnosis of pancreatic cystic lesions. A prospective study of 28 percutaneous aspirates. Acta Cytol 1997; 41:972-80. [PMID 9250287]

24. Zamboni G, Longnecker DS, Klöppel G. Mucinous cystic neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, Eds. Pathology and Genetics of Tumors of the Digestive System. Lyon, France: IARC Press; 2002:234-6.

25. Adsay NV, Klimstra DS. Cystic forms of typically solid pancreatic tumors. Semin Diagn Pathol 2000; 17:81-8. [PMID 10721809]

26. Pais SA, Attasaranya S, Leblanc JK, Sherman S, Schmidt CM, DeWitt J. Role of endoscopic ultrasound in the diagnosis of intraductal papillary mucinous neoplasms: correlation with surgical histopathology. Clin Gastroenterol Hepatol 2007; 5:489-95. [PMID 17350894]

27. Brandwein SL, Farrell JJ, Centeno BA, Brugge WR. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. Gastrointest Endosc 2001; 53:722-7. [PMID 11375578]

28. Satoh K, Kaneko K, Hirota M, Toyota T, Shimosegawa T. The pattern of CPP32/caspase-3 expression reflects the biological behaviour of the human pancreatic duct cell tumors. Pancreas 2000; 21:352-7. [PMID 11075989]

29. Kitagawa Y, Unger T, Taylor S, Kozarek R, Traverso L. Mucus is a predictor of better prognosis and survival in patients with intraductal papillary mucinous tumor of the pancreas. J Gastrointest Surg 2003; 7:12-18. [PMID 12559180]

30. Kawahira H, Kobayashi S, Kaneko K, Asano T, Ochiai T. p53 protein expression in intraductal papillary mucinous tumors (IDMT) of the pancreas as an indicator of tumor malignancy. Hepatogastroenterology 2000; 47:973-7. [PMID 11020860]

31. Adsay N, Merati K, Basturk O, Iacobuzio-Donahue C, Levi E, Cheng JD, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: deliniation of an "intestinal" pathway of carcinogenesis in the pancreas. Am J Surg Pathol 2004; 28:839-48. [PMID 15223952]

32. Yonezawa S, Nakamura A, Horinouchi M, Sato E. The expression of several types of mucin is related to the biological behaviour of pancreatic neoplasms. J Hepatobiliary Pancreat Surg 2002; 9:328-41. [PMID 12353144]

33. Satoh K, Sasano H, Shimosegawa T, Koizumi M, Yamazaki T, Mochizuki F, et al. An immuno-histochemical study of the c-erbB-2 oncogene product in intraductal mucin-hypersecreting neoplasms and in ductal cell carcinomas of the pancreas. Cancer 1993; 72:51-6. [PMID 8099533]