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Pancreatic cyst fluid concentration of high-mobility group A2 protein acts as a differential biomarker of dysplasia in intraductal papillary mucinous neoplasm

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Abstract

Background and Aims—No reliable cyst fluid biomarkers exist that allow for the pre-operative identification of patients with intraductal papillary mucinous neoplasms (IPMN) and high-risk pathology. High-mobility group A2 (HMGA2) proteins have been demonstrated to be a biomarker of dysplasia in IPMN. It is unknown whether HMGA2 is present in the cyst fluid from IPMN. The aims of this study were to determine if HMGA2 protein is present in the cyst fluid of IPMN, and demonstrate if HMGA2 concentration correlates with degree of dysplasia.

Methods—Patients with surgically resected IPMN and banked pancreatic cyst fluid were identified. Low-risk IPMN (low-grade [LGD] or moderate dysplasia [MD]), and high-risk IPMN (high-grade dysplasia [HGD] or invasive cancer) were identified. Pancreatic cyst fluid concentrations of HMGA2 were measured via ELISA.

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Results—Samples from 31 patients were analyzed. HMGA2 protein was detected in the cyst fluid of 30/31 (97%) specimens. Median cyst fluid HMGA2 concentration (ng/mL) was as follows: LGD 0.6 (IQR: 0.35-0.6), MD 1.55 (IQR: 0.65-2.7), HGD 4.2 (IQR: 1.7-9.2) ($p < 0.05$). The median HMGA2 concentration was significantly higher in the HGD group (4.2 ng/mL, IQR 1.7-9.2) compared with the concentration in the low-risk group (1.1 ng/mL, IQR 0.6-2.7, $p = 0.03$).

Conclusions—HMGA2 protein is present in IPMN cyst fluid. Significantly higher concentrations of cyst fluid HMGA2 proteins are found in IPMN with HGD as compared with lesions with LGD or MD. Cyst fluid concentrations of HMGA2 may thus serve as a biomarker to differentiate patients with high-risk IPMN from patients with low-risk IPMN.

Introduction

Branch duct intraductal papillary mucinous neoplasms (BD-IPMN) are a type of pancreatic cystic lesion, which can exhibit the full spectrum of pathologic features, from low-grade dysplasia to invasive cancer (1,2). The prevalence of BD-IPMN in the United States is estimated to be approximately 2.5%, with upward of 2 million people having one (3-5). Given that these lesions have the potential for malignant transformation, surgical resection should be considered in appropriate candidates (6). However, the preoperative identification of patients with BD-IPMN and high-risk pathology who would thus benefit from surgical resection continues to prove difficult.

The current state-of-the-art approach to correctly characterize a particular pancreatic cystic neoplasm rests on cytological, chemical, and molecular analysis of the pancreatic cyst fluid. Unfortunately, the current applications in use are insufficient in detecting whether malignancy is present. As such, many patients undergo resection of benign cystic neoplasms. An easily measurable, pancreatic cyst fluid biomarker of dysplasia or carcinoma would be critical in identifying those patients who would benefit most from surgical resection. Thus far, no such dependable biomarker exists.

High-mobility group (HMG) proteins have the potential to be a biomarker of dysplasia or carcinoma in pancreatic cystic neoplasms. HMG proteins are architectural factors that bind to active chromatin and affect transcription. Over-expression of these proteins has been demonstrated to be a marker of high-grade epithelial dysplasia in a variety of malignant tumors, including pancreatic adenocarcinomas and pancreatic cystic neoplasms (7-13). HMG group A2 (HMGA2) proteins have been demonstrated to be a biomarker of dysplasia in surgical pathology specimens of IPMN (14).

We have previously reported the results of a small pilot study examining HMGA2 expression in both benign and malignant pancreatic lesions, including pancreatic cystic neoplasms (15). Based on the results of that pilot study, we sought to examine whether HMG proteins were present in pancreatic cyst fluid. If HMG proteins are present in the fluid of pancreatic cystic neoplasms, it may act as a biomarker of dysplasia or carcinoma. Given that pancreatic cyst fluid is readily accessible and chemical analysis is routinely performed, an HMG protein biomarker would serve as an easily measurable, dependable diagnostic tool in the evaluation of pancreatic cystic neoplasms. This would certainly have a role in

stratifying those patients who would benefit most from surgical resection, and thus avoid the resection of benign lesions.

The aim of this study was to determine whether HMGA2 protein is present in the cyst fluid of IPMN, and demonstrate whether HMGA2 concentration correlates with degree of dysplasia.

Materials and Methods

Patients eligible for inclusion in this study were those with surgically resected IPMN who also had corresponding banked pancreatic cyst fluid. Patients were preoperatively consented for collection and storage of tissue as part of an institutional review board (IRB)-approved tissue procurement protocol. IRB approval was granted to retrospectively identify patients eligible for this study as well as for analysis of data. Permission was granted from the institutional human biospecimen utilization committee to perform biomedical analysis of the banked specimens.

Pancreatic cyst fluid was obtained via aspiration at the time of surgical resection. Cyst fluid samples were divided into 500 μ L aliquots and stored at -80° C. All analyses were performed on samples with no prior freeze-thaw cycles.

Patients with a surgically resected IPMN and corresponding banked cyst fluid were identified. IPMN subtypes included branch duct, main duct, and mixed type (containing both branch duct and main duct components). IPMN were classified as either low-risk lesions or high-risk lesions. Low-risk IPMN were classified as those with low-grade dysplasia (LGD) or moderate dysplasia (MD). High-risk IPMN were classified as those containing high-grade dysplasia (HGD) or invasive cancer. Grading of dysplasia in the IPMN was based on the most severe degree of dysplasia present in the pathologic specimen.

Pancreatic cyst fluid concentrations of HMGA2 were measured via a commercially available enzyme-linked immunosorbent assay (ELISA) (Uscn Life Sciences, Inc., Houston, Tex). All samples were run according to the manufacturer's specifications.

Statistical analysis was performed using a Wilcoxon two-sample test. Nonparametric variables were reported as medians with interquartile ranges (IQR). A p value < 0.05 was considered significant. A receiver operator curve (ROC) was calculated for HMGA2.

Results

A total of 31 patients were identified; males 16 (52%), mean age 72 years. IPMN types were branch duct (n = 19), main duct (n = 6), mixed type (n = 4), and not listed (n = 2). LGD was present in 3 patients, MD in 18 patients, HGD in 9 patients, and invasive cancer in 1 patient.

BD-IPMN size was available for 16 of the 23 (70%) BD or mixed type IPMN median size according to dysplasia type: LGD 3.4 cm (n = 1), MD (n = 11) 3.4 cm (range: 1.5 – 6.0), HGD (n = 5) 4.0 cm (range: 1.5 – 6.5). HMGA2 protein was detected in the cyst fluid of 30/31 (97%) specimens. Median cyst fluid HMGA2 concentration (ng/mL) was as follows:

LGD 0.6 (IQR: 0.35-0.6), MD 1.55 (IQR: 0.65-2.7), HGD 4.2 (IQR: 1.7-9.2) ($p < 0.05$) (Figure 1). No HMGA2 was detected in the one sample from IPMN with invasive cancer. The median HMGA2 concentration was significantly higher in the HGD group (4.2 ng/mL, IQR 1.7-9.2) compared with the concentration in the low-risk group (1.1 ng/mL, IQR 0.6-2.7, $p = 0.03$). The ROC for HMGA2 had an area under the curve of 0.74.

Discussion

IPMN is a type of pancreatic cystic lesion that is being increasingly recognized in clinical practice (5). These neoplastic lesions exhibit the full spectrum of cellular atypia, from low-grade and moderate dysplasia to high-grade dysplasia and invasive cancer. Given this risk, the identification of an IPMN represents an important opportunity to identify patients at increased risk of developing pancreatic cancer and thus intervene before the development of malignancy.

Current diagnostic evaluation and characterization of IPMN relies on the analysis of pancreatic cyst fluid obtained at the time of EUS-FNA. Unfortunately, given the paucicellular nature of this fluid, cytologic analysis is largely unreliable, with very low sensitivity and accuracy (16-19). Cyst fluid biomarkers hold more promise as a potential diagnostic tool. For example, cyst fluid CEA levels are currently the most accurate tool that allows for differentiation of mucinous pancreatic cysts from non-mucinous ones (17, 20). However, the cyst fluid CEA concentration does not correlate with the presence or risk of developing malignancy in any particular IPMN (17, 21). Similarly, the metabolomics-derived cyst fluid biomarkers of glucose and kynurenine have shown promise in their ability to differentiate mucinous from non-mucinous pancreatic cysts. Yet, fluid concentrations of these metabolites did not differentiate malignant mucinous cysts from non-malignant ones (22). In recent years, a number of cyst fluid biomarkers have been identified that hold promise in their ability to differentiate low-risk IPMN from high-risk IPMN. A study examining various interleukins has demonstrated that interleukin 1 β was able to correctly differentiate high-risk IPMN from low-risk IPMN (23). Cyst fluid prostaglandin E2 levels have shown similar potential in both branch duct and main duct IPMN (24). However, neither of these biomarkers has been validated in large, prospective studies, and thus they remain experimental at this time. Regardless, the identification and validation of these and other such biomarkers could assist clinicians in determining which patients may benefit from surgical resection of an IPMN, versus management with radiographic and/or endoscopic surveillance.

High-mobility group proteins have the ability to be a biomarker of dysplasia or carcinoma in IPMN. HMG proteins are architectural factors that bind to active chromatin and affect transcription. The HMGA family of these proteins are characterized by having “A-T” hooks, which bind to A-T rich regions of chromatin and elicit their effect. HMGA1 and HMGA2 proteins are the products of the HMGA1 and HMGA2 gene, respectively. These proteins are present in stem cells, with their main role in cell proliferation and differentiation during embryogenesis (25). As such, HMGA expression is negligible in normal adult tissue (26).

Over-expression of HMGA proteins has been demonstrated in a variety of tumors. For example, HMGA1 over-expression has been demonstrated in esophageal cancer, colon cancer, pancreatic cancer, and IPMN (7-10). In addition, the over-expressed protein can be detected in pre-malignant stages of these cancers, with higher expression correlating with higher degree of cellular atypia in Barrett's esophagus, colonic adenomas, and IPMN (7-10). Similarly, HMGA2 over-expression has been demonstrated in a variety of tumors. HMGA2 expression was 160-fold higher in oral squamous cell carcinomas, compared with normal gingival tissue, and disease-free survival was significantly worse in patients with HMGA2-positive tumors (11). Rogalla et al (12) demonstrated that degree of immunohistochemistry positivity correlates to higher histologic grades of breast cancer. HMGA2 was observed to be present in the peripheral blood of breast cancer patients with metastatic disease, but absent in healthy donors and those with localized disease (13).

In regard to HMGA2 proteins and pancreatic disease, Abe et al demonstrated that HMGA2 expression is detectable in pancreatic adenocarcinoma by IHC (27/27, 100%), but absent in normal pancreatic tissue (0/6, 0%) and chronic pancreatitis specimens (0/2, 0%) (14). We have previously reported the results of a small pilot study examining HMGA2 expression in both benign and malignant pancreatic lesions, including pancreatic cystic neoplasms. Immunohistochemistry testing for HMGA2 expression on pathologic specimens demonstrated absence of HMGA2 in serous cystadenoma (0/2, 0%) and benign mucinous cystic neoplasms (0/2, 0%), but positive detection in IPMN with invasive cancer (2/2, 100%) and pancreatic adenocarcinoma (2/2, 100%) (Figure 3) (15). These findings supported our hypothesis that HMGA2 is not expressed in benign/low-risk lesions, but is expressed in high-risk/malignant pancreatic lesions.

In the present study, we sought to determine if HMGA2 protein is present in the cyst fluid of IPMN, and whether the concentration of cyst fluid HMGA2 has any correlation with degree of cellular atypia within the cyst lining. HMGA2 protein was demonstrated to be present in pancreatic fluid associated with branch duct IPMN, main duct IPMN, and mixed type IPMN.

Furthermore, this protein was detected in nearly all samples tested (30/31, 97%) by use of a commercially available ELISA. Perhaps most important, all testing was performed on fluid samples of only 500 uL. This is extremely pertinent, as cyst fluid samples are often limited in quantity, particularly if being used for multiple analytic tests. Our results also demonstrate that cyst fluid concentrations of HMGA2 positively correlate with the most severe level of dysplasia exhibited by the IPMN specimens on surgical pathology. As was demonstrated in previously referenced studies involving HMGA protein expression in various tumor types (eg, Barrett's, colon cancer, breast cancer), our results expectedly demonstrated a significant difference in cyst fluid HMGA2 concentrations among the low-grade, moderate-grade, and high-grade dysplasia sub-types, with more severe atypia associated with higher protein concentration. Last, when classifying the IPMN samples into low-risk or high-risk lesions (based on degree of dysplasia), there was a significantly higher level of cyst fluid HMGA2 protein in the high-risk lesions. This finding ultimately supports the notion that cyst fluid HMGA2 may in fact be a suitable biomarker of dysplasia and thus risk of malignant transformation.

It is noted that HMGA2 was not detected in the one fluid sample from an IPMN with invasive cancer. It is unclear why this specimen was negative for the biomarker. It is noted that fluid obtained from this lesion at the time of EUS-guided fine-needle aspiration was too viscous for standard pancreatic cyst fluid analysis (ie, CEA), and thus this is the most likely reason that HMGA2 analysis led to a presumably false-negative result.

There are a number of strengths and limitations with this study. Perhaps the most important strength of this study is that all investigations were based on true surgical pathology results from resected IPMN specimens. Current non-operative diagnostic sampling methods for IPMN are limited to cytologic, molecular, and chemical analysis, which is wrought with poor accuracy and thus may lead to under-staging of dysplasia severity given the paucicellular nature of cyst fluid. The main limitations of this study pertain to the relatively small sample size and suboptimal distribution of dysplasia sub-types. For example, the study population only had one specimen with invasive cancer, which was negative for the cyst fluid biomarker. A proper biomarker of dysplasia ultimately is only as good as its ability to correlate with cancer. Thus, our study was sorely lacking this important element. Furthermore, this likely contributed to the only moderate results of the ROC (0.74). Ultimately, our current proof-of-principle study would ideally be validated with a prospective study involving a large number of patients. A larger sample size would allow for a better distribution of pathologic subtypes, particularly IPMN with invasive cancer. This, however, will remain a challenge because fewer lesions are being resected, and thus it will remain difficult to correlate cyst fluid analysis results with surgical pathology specimens. A major issue that future studies should focus on is whether or not cyst fluid HMGA2 can be detected in cyst fluid samples obtained at the time of EUS-FNA. In addition, cyst fluid analysis results should be correlated with specific patient demographics, symptoms, radiographic, and endoscopic findings, including presence of high-risk or worrisome features such as cyst size, presence of intramural nodules, and presence of pancreatic duct dilation (6). This was a major limitation to our study, as complete data on the presence of mural nodules and a dilated pancreatic duct were known in only 17 of 31 (55%) of cases, and information pertaining to preoperative cyst size was available in only 21 of 31 (68%) of cases; in addition, cyst fluid CEA levels were known for only 8 of 23 (35%) of BD-IPMN or mixed-type IPMN, and thus no meaningful correlation could be assessed. Last, the presence of this cyst fluid biomarker and how it relates to patient survival would be the ultimate performance test. Numerous studies have demonstrated that HMGA protein expression in pancreatic adenocarcinoma correlates with advanced tumor grade and lymph node metastases, and may also play a role in resistance to specific chemotherapeutic agents (27-29).

In conclusion, HMGA2 protein is present and detectable in the cyst fluid of IPMN. Significantly higher concentrations of cyst fluid HMGA2 proteins are found in IPMN with HGD as compared with lesions with LGD or MD. Cyst fluid concentration of HMGA2 may potentially serve as a biomarker to differentiate patients with high-risk IPMN lesions from low-risk lesions.

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Acronyms

BD-IPMN	branch duct intraductal papillary mucinous neoplasm
IPMN	intraductal papillary mucinous neoplasm
HMG	high-mobility group
HMGA2	high-mobility group A2
LGD	low-grade dysplasia
MD	moderate dysplasia
HGD	high-grade dysplasia
IRB	institutional review board
ELISA	enzyme-linked immunosorbent assay

ROC receiver operator curve

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Figure 1.
Median concentration of HMGA2 (ng/ml) in IPMN cyst fluid by grade of dysplasia.

Figure 2. Median concentration of HMGA2 (ng/ml) in IPMN cyst fluid, low-risk lesions vs high-risk lesions.

Figure 3. Immunohistochemistry staining for HMGA2 in pathology specimens: Negative staining in benign mucinous cystic neoplasm (A); positive staining in intraductal papillary mucinous neoplasm with invasive cancer (B) and pancreatic adenocarcinoma (C).