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

Methods: Patients with surgically resected IPMNs and banked pancreatic cyst fluid were identified. Low-risk IPMNs (low-grade [LGD] or moderate dysplasia [MD]) and high-risk IPMNs (high-grade dysplasia [HGD] or invasive cancer) were identified. Pancreatic cyst fluid concentrations of HMGA2 protein were measured via enzyme-linked immunosorbent assay.

Results: Samples from 31 patients were analyzed. HMGA2 protein was detected in the cyst fluid of 30 of 31 specimens (97%). Median cyst fluid HMGA2 protein concentration (ng/mL) was as follows: LGD, 0.6 (interquartile range [IQR] 0.35-0.6); MD, 1.55 (IQR 0.65-2.7); HGD, 4.2 (IQR 1.7-9.2) ($P < .05$). The median HMGA2 protein 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, $P = .03$).

Conclusion: HMGA2 protein is present in IPMN cyst fluid. Significantly higher concentrations of cyst fluid HMGA2 protein are found in IPMNs with HGD compared with lesions with LGD or MD. Cyst fluid concentrations of HMGA2 protein may thus serve as a biomarker to differentiate patients with high-risk IPMNs from those with low-risk IPMNs. (Gastrointest Endosc 2016;83:1205-9.)

A branch duct intraductal papillary mucinous neoplasm (BD-IPMN) is a type of pancreatic cystic lesion that can exhibit the full spectrum of pathologic features, from low-grade dysplasia (LGD) 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

Abbreviations: BD-IPMN, branch duct intraductal papillary mucinous neoplasm; CEA, carcinoembryonic antigen; HGD, high-grade dysplasia; HMG, high-mobility group; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; LGD, low-grade dysplasia; MD, moderate dysplasia.

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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 a 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. Overexpression 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] HMGA2 protein has been demonstrated to be a biomarker of dysplasia in surgical pathology specimens of IPMNs.[14]

We 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, they 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 resection of benign lesions.

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

MATERIALS AND METHODS

Patients eligible for inclusion in this study were those with surgically resected IPMNs who also had corresponding banked pancreatic cyst fluid. Preoperatively, patients were consented for collection and storage of tissue as part of an institutional review board–approved tissue procurement protocol. Institutional review board 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-μL aliquots and stored at −80°C. All analyses were performed on samples with no previous 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). IPMNs were classified as either low-risk or high-risk lesions. Low-risk IPMNs were classified as those with low-grade dysplasia (LGD) or moderate dysplasia (MD). High-risk IPMNs 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 (USCN Life Science, Inc, Houston, Tex). All samples were run according to the manufacturer's specifications.

Statistical analysis was performed by using a Wilcoxon 2-sample test. Nonparametric variables were reported as median with interquartile range (IQR). A P value <.05 was considered significant. A receiver-operating characteristic curve was calculated for HMGA2.

RESULTS

A total of 31 patients were identified: 16 male patients (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.

Size was available for 16 of the 23 BD-IPMNs or mixed-type IPMNs (70%); median size according to dysplasia type: LGD, 3.4 cm (n = 1); MD, 3.4 cm (range 1.5–6.0), n = 11; HGD, 4.0 cm (range 1.5–6.5), (n = 5). HMGA2 protein was detected in the cyst fluid of 30 of 31 specimens (97%). 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 < .05) (Fig. 1). No HMGA2 protein was detected in the 1 sample from the IPMN with invasive cancer. The median HMGA2 protein 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 = .03) (Fig. 2). The receiver-operating characteristic curve for HMGA2 protein had an area under the curve of 0.74.