ACS Case Reviews in Surgery
Vol. 1, No. 5

Management of a Complex Multifocal Intraductal Papillary Mucinous Neoplasm

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Background	A male patient with multifocal intraductal papillary mucinous neoplasm (IPMN) treated outside of consensus guidelines based on comorbidities and family history that may impact malignant potential.
Summary	Our patient is a 64-year-old male with type 2 diabetes mellitus (DM) and a history of pancreatic adenocarcinoma in a first-degree relative, who was incidentally found to have multiple pancreatic cysts. Subsequent magnetic resonance cholangiopancreatography (MRCP) identified five cystic lesions throughout the body, tail and uncinate process of the pancreas. Endoscopic ultrasound-guided fine needle aspiration (EUS/FNA) of the dominant cyst demonstrated elevated carcinoembryonic antigen and amylase levels, consistent with multifocal branch duct IPMN (BD-IPMN). In this setting however, the patient elected for resection with total pancreatectomy and splenectomy, which was performed in an uncomplicated fashion. Thirty-three months following the operation, the patient has maintained a good quality of life with reasonable diabetic control. Departure from consensus guidelines was influenced by the patient's combined history of diabetes and a first-degree relative with pancreatic cancer, both of which increase the likelihood of malignancy in IPMN.
Conclusion	Management of BD-IPMN remains controversial with separate Fukuoka and European consensus guidelines that generally recommend conservative management of multifocal BD-IPMN in the absence of symptoms or imaging features to suggest malignancy. The influence of DM and family history on the malignant potential of IPMN remains ill-defined. We present a patient with DM (and who has a single first-degree relative with pancreatic adenocarcinoma) who elected to have a total pancreatectomy outside of consensus guidelines. Additionally, this case report further examines the data that support multifocal IPMN management.
Keywords	Pancreas, cystic lesion of pancreas, intraductal papillary mucinous neoplasm, IPMN, branch duct, diabetes mellitus, familial pancreatic cancer

DISCLOSURE:
None of the authors have any conflicts of interest, financial or otherwise, to disclose which may have influenced the completion of this project.

Permission to use and publish the results of the FACT-Hep survey was obtained Functional Assessment of Chronic Illness Therapy (FACIT).

Informed consent was obtained from the patient described in this report.

ACKNOWLEDGEMENTS:
Cheryl I. Anderson, RN, BSN, MSA. Director, Quality Improvement and Surgical Education. Michigan State University College of Human Medicine Department of Surgery. 1200 E. Michigan Ave, Suite 655.

To Cite: Hardaway JC, Kanitra JJ, Kurane PH, Kavuturu S. Management of a Complex Multifocal Intraductal Papillary Mucinous Neoplasm. *ACS Case Reviews in Surgery.* 2018;1(5):1-4.

Case Description

A 64-year-old male presented after multiple pancreatic cysts were incidentally identified during computed tomography evaluation for bladder calculus. He has a 25-year history of hypertension and non-insulin dependent type 2 diabetes mellitus (T2DM). His mother was formerly diagnosed with pancreatic adenocarcinoma at an unknown age. Magnetic resonance cholangiopancreatography (MRCP) confirmed five cystic lesions (size range 1.1–2.2 cm) throughout the body, tail and uncinate process of the pancreas (Figure 1).

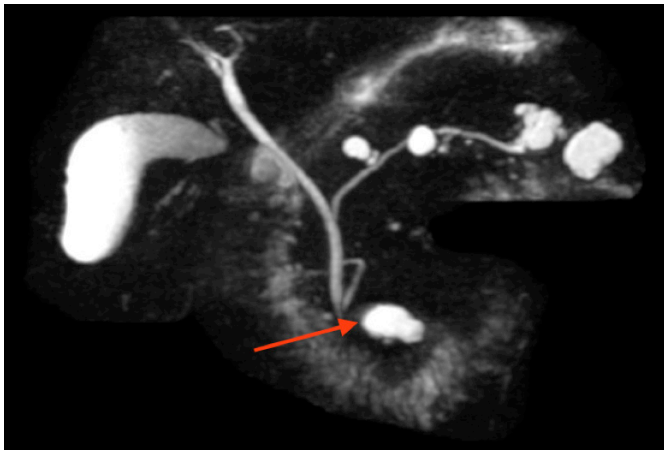

Figure 1. MRCP demonstrating five cystic lesions distributed throughout the pancreas, including an uncinate process cyst (arrow).

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of the dominant cyst demonstrated carcinoembryonic antigen (CEA) levels >2000 ng/mL and amylase levels >900 ng/ml, consistent with intraductal papillary mucinous neoplasm (IPMN). In the absence of main pancreatic duct dilatation (1.1 mm) or cystic nodular enhancement, he was diagnosed with multifocal branched duct IPMN without 'high-risk' stigmata or 'worrisome features'.[1] These findings were discussed with the patient in context of his family and medical history before he elected for total pancreatectomy and splenectomy.

Following an uncomplicated procedure, pathologic analysis identified multiple mucin filled cysts, the largest of which measured 2 cm. All IPMN were gastric type with low-grade dysplasia, but with multiple pancreatic intraepithelial neoplasia (PanIN) I-II admixed throughout the gland (Figure 2).

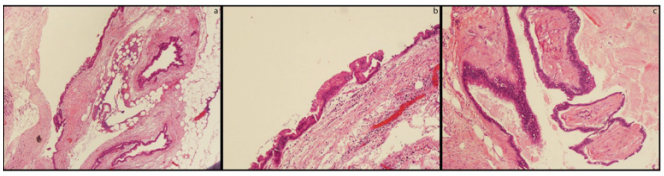

Figure 2. Hematoxylin and Eosin staining demonstrating gastric type epithelium with no or minimal cytologic atypia. **a** 40x **b** 100x **c** 100x

Eleven lymph nodes were negative for malignancy. On the basis of multifocal PanIN II lesions, the patient was not a candidate for islet auto-transplantation. Thirty-three months after his procedure, a quality of life assessment was done using the Functional Assessment of Cancer Therapy-Hepatobiliary survey (FACT-Hep©; available from FACIT.org), with a score of 148/180, indicating that the patient was functioning independently without pain and with good emotional well-being; however, a preoperative FACT-Hep survey is not available for comparison. His most recent HbA1c is 8.2 percent.

Discussion

IPMNs are typically identified in the 6th to 7th decade of life and are characterized by papillary neoplastic growths of mucin producing, columnar cells of the pancreatic ductal epithelium.[2] They are further classified as main duct (MD), branched duct (BD), or mixed-type, in relation to their localization and extension within the pancreatic ductal system.[3] Due to a high rate of malignant transformation among MD-IPMNs (33–62 percent), segmental pancreatectomy with lymph node dissection is recommended.[3,4] A more conservative approach is considered for BD-IPMNs, among which 11–30 percent of resected cases are malignant.[3] Mixed-type IPMNs harbor malignancy risks close to that of MD-IPMNs, hence are managed similarly.[4]

Fukuoka consensus guidelines (FCG) for BD-IPMNs state that patients without "high-risk stigmata" (enhancing solid component, main pancreatic duct size ≥10 mm, or obstructive jaundice secondary to cystic lesion) or "worrisome features" (cyst ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, main pancreatic duct size 5–9mm, abrupt change in main pancreatic duct caliber with distal pancreatic atrophy and lymphadenopathy) can be surveilled with a combination of computed tomography (CT)/MRCP/EUS, as indicated.[3] FCG further suggest treating multifocal BD-IPMN in the same manner as unifocal BD-IPMNs, with targeted evaluation and/or

resection of the cyst with highest oncologic potential, but that total pancreatectomy may be considered in patients with a strong family history of pancreatic cancer. Application of FCG to our patient favors surveillance with EUS at 3–6 months, then lengthening intervals with alternation between MRCP and EUS.

European consensus guidelines (ECG) on BD-IPMN management propose absolute indications (pancreatic symptomatology, mural nodules, or dilation of the main pancreatic duct >6mm diameter) and 'relative indications' (rapidly increasing size and elevated serum levels of CA 19–9) for BD-IPMN resection.[4] For multifocal IPMNs, ECG also recommend evaluation and treatment of each cyst autonomously. In sum, ECG favors surveillance imaging in our patient as opposed to immediate resection. Despite mutual recommendation for surveillance by both the FCG and ECG, the combination of pre-existing DM and a single first-degree relative with history of pancreatic adenocarcinoma lowered our threshold to recommend surgical resection.

While FCG/ECG both consider patient symptoms such as jaundice or pancreatitis in the context of the radio-/sonographic features of BD-IPMNs, ECG includes DM as an 'absolute indication' for resection, but doesn't clearly delineate between 'new onset' and 'preexisting' diabetes. The 'dual causality' between T2DM and pancreatic adenocarcinoma is well evidenced across multiple clinical and epidemiological studies.[5] Only recently has the association between DM and IPMN with either high-grade dysplasia (HGD) or invasive carcinoma been suggested. Morales-Oyarvide et al reported that resected IPMN from DM patients had a significantly higher risk of HGD (OR 2.02) and invasive carcinoma (OR 2.05) when adjusting for 'worrisome features' in a multivariate analysis.[6] The significance of this finding for DM did not hold true when adjusting for 'high-risk stigmata,' suggesting that DM has greater predictive value among cysts with lower malignant potential. The subtlety in evaluating associations between DM and HGD versus invasive carcinoma among the FCG/ECG criteria is significant in terms of gauging when to intervene among BD-IPMN patients, since those with HGD at resection have >95 percent disease-specific survival, while those who manifest invasive carcinoma have a worse prognosis with a 40 percent 5-yr OS. In light of these findings, a history of DM may warrant consideration in the next iteration of the guidelines.

While there has been extensive study of familial pancreatic cancer (FPC), defined as at least two first degree relatives with pancreatic adenocarcinoma (PDAC), there is very little evidence to guide the management of IPMN patients with a family history of PDAC.[7] FCG cite a 2.3-, 6.4-, and 32-fold increased risk of developing PDAC on the basis of having one, two, or three first-degree relatives with PDAC, respectively; however, the guidelines only modestly incorporate family history—patients with single affected first-degree relatives are followed similar to those without family history and those with two or more affected first-degree relatives warrant 'more aggressive' surveillance but shouldn't influence recommendation for resection. ECG on the other hand, cite an incomplete understanding of familial influence on the natural history of IPMN, and thus omit this element from consideration. A study from a prospectively collected FPC registry in Germany argues otherwise, wherein a clinicopathologic analysis was performed among multifocal IPMN patients who underwent surgical resection outside of consensus guideline recommendations. Four out of five patients underwent total pancreatectomy with similar pathology seen in all five patients, for what is described as gastric-type BD-IPMNs with low to moderate dysplasia and multifocal moderate to high-grade PanIN lesions that were distinct from the IPMN and were not observable on preoperative imaging.[8] Despite the small sample size, the uniformity of these observations, which is observed in our patient with a single first-degree relative, suggests that any family history of PDAC should be given further consideration in the treatment algorithm for multi-focal BD-IPMNs.

Conclusion

The Fukuoka and European consensus guidelines recommend conservative multifocal BD-IPMN management, despite malignant potential >25 percent. The two factors discussed here—diabetes mellitus and a first-degree family member with history of PDAC—suggest an increase in the malignant potential of multifocal BD-IPMNs, either within the IPMNs themselves or among high-grade PanIN lesions. The deference to surveil BD-IPMNs under the current guidelines, without consideration of these two factors, contrasts against the recommendation for resection of all MD-IPMNs, which has a 33 to 62 percent rate of malignant transformation. As we learn more of the natural history of an IPMN and its relation to DM and familial inheritance, the consensus guidelines are likely to incorporate these findings; however, until then, these clinical decisions will be made through a mutual decision making process by the patient and surgeon.

Lessons Learned

The Fukuoka and European consensus guidelines are the current standard for managing IPMNs, but it is important to realize they are not exhaustive. Surgeons must rely upon clinical judgment in some circumstances. Preexisting diabetes and a family history of pancreatic cancer are important considerations in the clinical decision to conservatively or surgically manage an IPMN.

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