Editorial

EUS and pancreatic cyst fluid analysis: Is the juice worth the aqueeze?

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With the rising identification of incidental pancreatic cystic lesions, clinicians must be aware of the complexity in their management. First, one must differentiate between neoplastic mucinous and nonmucinous cysts which are managed quite differently. Nonmucinous lesions may be inflammatory pseudocysts or neoplastic such as serous cystadenomas, but if accurately characterized, most do not require resection or long term follow-up. On the contrary, mucinous neoplasms (comprised of mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN)) have a known premalignant potential, and therefore are either resected or monitored in a surveillance program.

The critical issue being faced in routine clinical practice is accurate preoperative characterization of cystic lesions. Histology remains the gold standard, but requires resection. Since that is impractical for most low risk lesions, imaging provides indirect evidence of morphology. Characterization of cyst fluid has been touted as a more accurate means define the nature of pancreatic cysts. Cyst fluid CEA obtained at time of endoscopic ultrasound fine needle aspiration (EUS/FNA) remains the most accurate test to distinguish mucinous from non-mucinous cysts, though its diagnostic accuracy remains roughly 80% (1). Unfortunately, the performance of cytology is poor as well, due in part to the lack of cellularity in aspirates (2). The fact that 1 in 5 patients may be incorrectly characterized by state of the art evaluation remains an enormous challenge in daily patient management leading experts to question the value of the test for routine cyst characterization.

In 2006, International Consensus Guidelines were developed by a team of experts to define management of cystic mucinous neoplasms (3). They emphasize that the decision to undergo surgical resection versus surveillance of a presumed neoplastic cyst should be tempered by the patient's wishes, comorbidities, life expectancy and the risk of malignancy versus the risk of surgery. If the patient is an appropriate surgical candidate, the guidelines recommend resection of all MCNs, any IPMN which involve the main duct or side-branch IPMN (SB-IPMN) which are symptomatic, have a solid component, or are greater than 3cm in size (3). Cysts without these worrisome features should be monitored by imaging at 6-12 month intervals. While these recommendations appear straightforward, there remain unresolved challenges in their application to patient management. According to the guidelines, one should distinguish between MCN and IPMN, and in particular focal SB-IPMN, since the former should be resected whereas the latter can be monitored.

To date, imaging alone or combined with a battery of tests (fluid analysis, serum markers) fail to adequately addresses these challenges. Thus guidelines must rely on a presumptive diagnosis based on imperfect tools, which as expected, lead to imperfect selection of patients for surgical intervention. Given the morbidity and mortality of pancreatic surgery, it is not surprising efforts to better select patients for resection are a source of active investigation.

Al-Rashdan et al. attempt to critically evaluate this confusing maze of data and ask whether cyst fluid analysis really addresses this unmet clinical quandary of how to appropriately select patients with pancreatic cysts for surgery (4). They focus on the challenge to distinguish between mucinous subtypes by evaluating cyst fluid CEA and amylase. In the 10 year study period, they identified

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134 patients with pancreatic cysts who underwent surgical resection. Of these patients, 82 underwent a preoperative EUS. Sixty-six of the 82 were mucinous cysts (14 MCN, 52 IPMN). Of these 66, 25 had preceding FNA and cyst fluid analysis performed (9 MCN, 11 SB-IPMN and 5 main duct IPMN). The median and mean CEA were not statistically different between the 9 MCN and all 16 IPMN (p=0.19), as well as, MCN and SB-IPMN (p=0.34). The median and mean amylase were not statistically different between the MCN and all IPMN (p=0.64) and MCN and SB-IPMN (p=0.92). Of note, no data was provided regarding cross-sectional imaging or EUS findings.

Their data is similar to other studies that have found limitations in the accuracy of cyst fluid CEA and amylase--as well as its selective utilization in practice. In a cohort of 33 mucinous cystadenomas and 235 IPMN patients (5), Slozek et al. showed that neither CEA nor amylase was unable to distinguish between mucinous cystadenomas and IPMN (p=0.26 and 0.23 respectively). However, for this study, how many of the pathologic diagnoses were confirmed by surgical pathology or how the definition of mucinous cystadenoma was made was not provided. Curiously, cyst fluid CA19-9 was noted to distinguish mucinous cystadenomas and IPMN (p=0.003) (5). The elevated CA19-9 raises the possibility of a different biomarker to distinguish between types of mucinous cysts. Another study of 14 MCN and 52 IPMN cases confirmed by surgical pathology reported median CEA of 2844 ng/ml (range 1-14,500) in MCN and 574 ng/ml (0-38,500) in IPMN (5). While statistical analysis of this difference was not reported, the overlap between CEA concentrations is readily apparent. Most recently, in a study of 126 patients, Park et al. reported overlapping median values cyst fluid CEA between MCN and IPMN (428ng/ml [interquartile range IQR: 44-7870] and 414ng/ml [IQR 102-1223]), again without statistical analysis (7). Median values (and IQR) for cyst fluid amylase overlapped as well for MCN and IPMN (6800 IU/L [IQR 70-25,295] and 5090 IU/L [IQR 1119-38,290], respectively) (7).

The data from Al-Rashdan et al. adds to the growing body of evidence that cyst fluid analysis (CEA and amylase) alone is disappointing in its ability to distinguish between the mucinous lesions, MCN and IPMN. However, the question is we would ever look at cyst fluid analysis alone to make our clinical decisions? The answer is probably not.

The ability to distinguish clinically between the two mucinous types requires a broader perspective whereby imaging and patient factors play a well-documented role. Crippa et al. highlight the clinical and demographic differences between 168 patients with MCN and 159 with branch-duct IPMN (8). Patients with MCN were significantly younger (median 44.5 v. 66 yo, p=0.001) and almost exclusively women (95% v 57%, p=0.01) (8). MCN were most likely to be distal (97% v 25%, p =0.001) and were more likely to present with abdominal pain (62% v 45%, p=0.004) (8). IPMNs were also more likely to have a family history of pancreatic cancer (11% v 3.5%, p=0.01) and a history of other neoplasms (20 v 9%, p=0.006) (8). Moreover, MCN are thought to be separate from the main pancreatic duct whereas side-branch IPMNs are connected to the main duct. Of course, distinguishing MCN from SB-IPMN is not always so straightforward as MCN are reported to be connected to the main duct in up to 20% of cases (9).

At the University of Michigan, as well as other expert centers, multidisciplinary care involving gastroenterologists, radiologists, and surgeons and oncologists have become a valuable addition to the care of patients with pancreatic cysts. Careful review of the patient's history in the context of cross-sectional imaging, surgical risks, and an estimate of malignancy risk are taken into account with regard to clinical decisions. EUS and FNA also play an important role but are used selectively—it may serve as a confirmatory role (fluid analysis supporting mucinous etiology or benign nonmucinous etiology) and for high resolution imaging to rule out any solid component (See Fig 1).

What the Al-Rashdan study fails to explore is the clinical context in which the cyst fluid analysis was drawn. We do not know demographic information, imaging findings, or symptoms of the patient. This kind of information is likely to have played a stronger role than cyst fluid analysis in distinguishing the two etiologies and in driving the decision for resection. For example, multifocal cystic disease or an isolated lesion in the tail in a male is almost certainly IPMN and may not need resection. The critical question is whether any type cyst fluid analysis can add incremental value for such patients—such as prediction of malignancy risk. This is particularly important in clinically equivocal cases, such as a woman with a solitary lesion in the body or tail whose lesion is not clearly distinct from the main duct. In its current state, CEA and amylase are clearly inadequate and better biomarkers clearly needed.

There are a number of recent investigations to evaluate other cyst fluid biomarkers that may aid in the differentiation of mucinous cyst types. Prostaglandin (2) has been shown to have increased expression in pancreatic cancer tissue over normal pancreatic tissue (10) and may also distinguish between types of mucinous cysts. One study demonstrated that cyst fluid PGE (2) concentrations were greater in IPMNs versus MCNs (2.2 ± 0.6 v. 0.2 ± 0.1 pg/mol, p<0.05) (11). However, there was noted to be an overlap in PGE (2) concentrations in benign MCNs and SCAs,

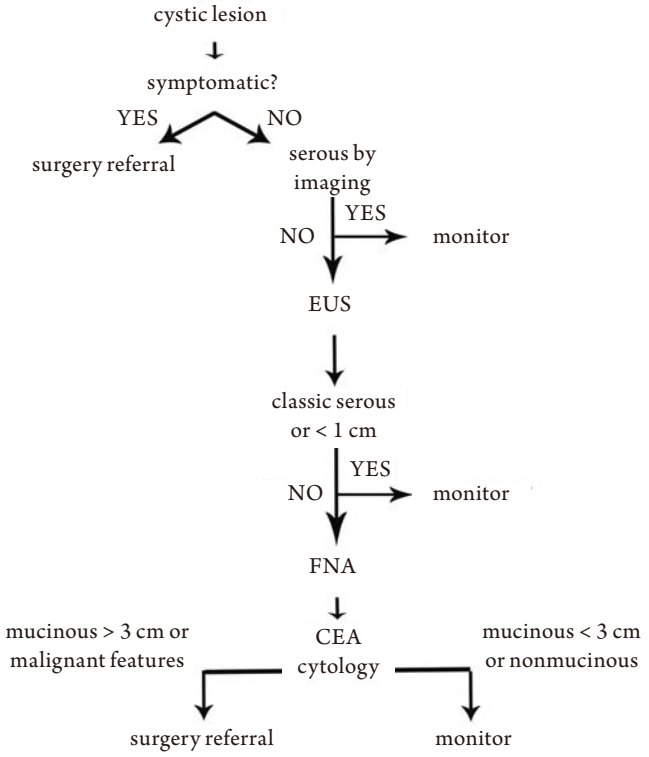

Figure 1 Clinical management of cystic lesion

thus limiting the utility of this biomarker in the clinical setting. These findings have not been validated in a larger study and will require further investigation before it is ready for clinical application.

Proteomic analysis of cyst fluid in a study of 8 patients who underwent surgical resection for symptomatic pancreatic neoplasms identified 92 proteins unique to MCNs and 29 unique to IPMNs (12). Analysis identified several proteins identified in the mucinous lesions (MCN and IPMN) that were previously reported to be up-regulated pancreatic cancer-associated proteins. The findings were confirmed by immunohistochemistry for two of the identified proteins, olfactomedin-4 (OLFM4) and the cell surface glycoprotein MUC18 (12). These are very promising preliminary data which will need to be validated in future studies.

Using a novel antibody-lectin sandwich array that targets glycan moieties on proteins (13), Haab et al. measured protein expression and glycosylation of MUC1, MUC5AC, MUC16, CEA, and other proteins associated with pancreatic cancer in 53 cyst fluid samples (14). Wheat germ agglutination of MUC5AC was markedly elevated in MCN and IPMN but not serous cystadenomas or pseudocysts. CA19-9 could distinguish between MCN and IPMN with a sensitivity and specificity of 82% and 93%, respectively. While these three aforementioned studies of biomarkers are not yet ready for "prime time", they show potential of molecular techniques to identify biomarkers that may prove more useful than CEA or amylase. Much larger sample sizes will be needed in future validation studies.

This JGO paper reemphasizes that the decision to send a patient with a pancreatic cyst for resection is complex, and requires a lot more than just EUS/ FNA with cyst fluid characterization. Their series confirms the results of others that amylase levels are of such limited value they likely should be abandoned. EUS/FNA does have small but measureable risks of bleeding, infection and pancreatitis; therefore, we agree with our Indiana University colleagues and suggest EUS-FNA with CEA levels should be used only when the results change management. We eagerly await the identification and development of future biomarkers which will make "the juice really worth the squeeze."

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