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Endosonographic Evaluation of Intraductal Papillary Mucinous Tumors of the Pancreas

Assaad Soweid, Cecilio Azar, Barbara Labban

Division of Gastroenterology, Department of Internal Medicine,
American University of Beirut Medical Center. Beirut, Lebanon

Introduction

Cystic neoplasms of the exocrine pancreas constitute a small fraction of pancreatic tumors. Within that group of neoplasms, intraductal papillary mucinous tumors (IPMT) can be distinguished from mucinous cystic neoplasms and serous cystic neoplasms. IPMT, also referred to as mucinous ductal ectasia, is a mucus-producing pancreatic tumor characterized by a dilated main pancreatic duct (MPD), patulous ampullary orifice, and mucus secretion [1]. IPMT involves part of or the entire pancreatic duct.

Although IPMT is considered a precancerous lesion, the rate of progression from adenoma to carcinoma is usually slow [2]. The etiology is unclear, but there are several molecular abnormalities described in the pathogenesis of IPMT. These include the K-*ras* mutations [3], *p53* over-expression, *DPC4* expression [4], *MUC2* and *MUC5* mucin mRNA over-expression [5].

IPMT is more prevalent in men between 60-70 years of age. It commonly presents as recurrent episodes of acute pancreatitis, manifesting as abdominal pain, due to chronic intermittent obstruction of the pancreatic duct by both intraductal tumor growth and inspissated mucous secreted by the tumor [6]. Some patients are asymptomatic and are found incidentally by imaging studies for different reasons. IPMT is classified as main duct type (MDT-IPMT) and branch duct type (BDT-IPMT) according to the anatomical involvement [7]. MDT-IPMT accounts for 75% of all IPMT and is histologically more aggressive than BDT-IPMT [8].

Because of its favorable prognosis, an extensive diagnostic workup for IPMT should be performed in patients presenting with cystic lesions of the pancreas. This workup often leads to the diagnosis in addition to defining the predominant tumor location and size, although the extent of the ductal changes can only be established by histopathology. Surgical resection is the therapy of choice for IPMT. The type of resection depends upon the extent of the quantitative and qualitative ductal involvement. Total pancreatectomy is currently the treatment for an IPMT that comprises the entire main duct.

Data from Sohn *et al*. suggest that the five-year survival rate for those patients following resection of IPMT with invasive cancer is improved compared to those patients with resected pancreatic ductal adenocarcinoma in the absence of IPMT. Survival following resection of IPMT without invasive cancer (regardless of the degree of dysplasia) is good, but recurrent disease in the residual pancreas suggests that long-term surveillance is critical. Based on the age at resection data, there appears to be a 5-year lag time from IPMT adenoma (63 years) to invasive cancer (68 years) [9].

The Japan Pancreas Society performed a multi-institutional, retrospective study of

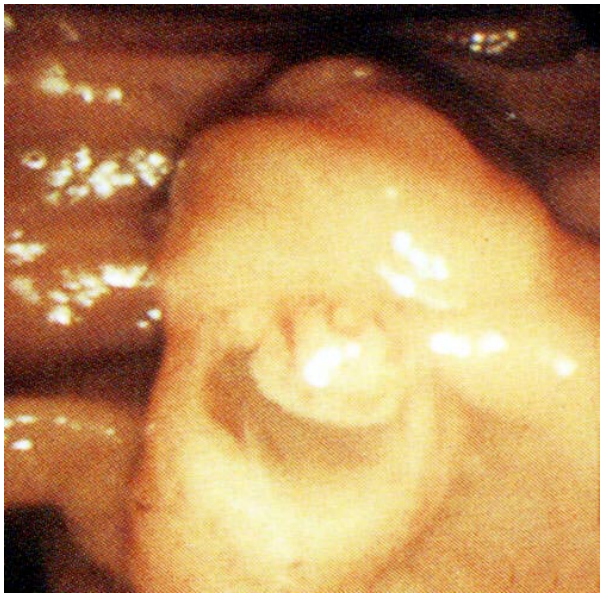

Figure 1. Endoscopic image of mucin oozing from the gaping orifice of the ampulla of Vater.

1,379 patients with IPMT. Clinico-pathological features and postoperative long-term outcomes were investigated. IPMT were most frequently found in men and in the head of the pancreas. Prognostic indicators of malignant IPMT included advanced age, presence of symptoms, abundant mucus secretion, presence of large nodules and/or large cysts, marked dilatation of the MPD, and main duct- or combined-type IPMT. The five-year survival rate of IPMT patients was 98-100% in adenoma to non-invasive carcinoma cases, 89% in minimally invasive carcinoma cases, and 58% in invasive carcinoma cases [10].

Diagnosis

There are different imaging modalities used in diagnosing IPMT but two or more tests are usually required to reach a more accurate diagnosis. Transabdominal ultrasound (US) and computed tomography (CT) alone cannot usually differentiate IPMT from diseases like mucinous cystic tumors of the pancreas, chronic obstructive pancreatitis, and pancreatic ductal adenocarcinoma. Endoscopic retrograde cholangiopancreato-graphy (ERCP) shows segmental or diffuse dilatation of the pancreatic duct, often with filling defects from mucus plugs [11]. The advantage of ERCP is the ability to obtain tissue sampling, and perform therapeutic maneuvers. A common scene is mucin oozing from the gaping orifice of the ampulla of Vater (Figure 1). Magnetic resonance cholangiopancreatography (MRCP) has a high diagnostic accuracy for IPMT and can reveal the full extent of ductal involvement particularly when obstructing mucus prevents diagnostic opacification of the MPD [12].

Endoscopic Ultrasonography

One of the advantages of endoscopic ultrasound (EUS) is the ability to apply the ultrasound transducer directly against the luminal surface, which minimizes intervening adipose tissue and air between the transducer and the target tissue, thereby enhancing image quality. The proximity of the transducer to the target tissue also permits the use of higher frequency ultrasound which further contributes to enhanced image resolution. As a result, EUS is routinely used in the evaluation of numerous gastrointestinal disorders, including the diagnosis and staging of gastrointestinal and pancreaticobiliary tumors.

The findings for IPMT on EUS include dilatation (segmental or diffuse) of the MPD with detection of intraductal (mural) nodules in MDT-IPMT (Figure 2) or multiple cysts in

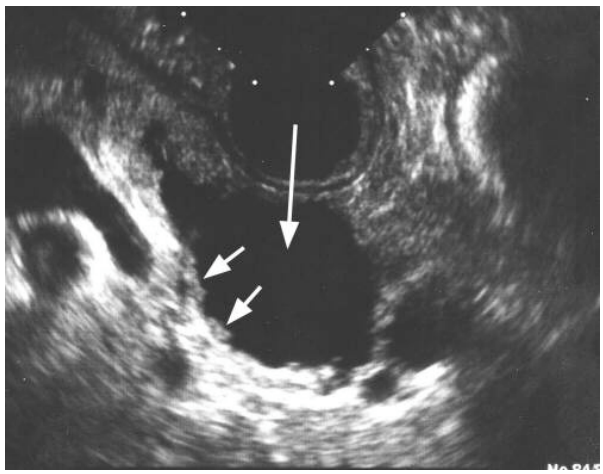

Figure 2. EUS image obtained with radial echoendoscope showing features of MDT-IPMT. These include dilatation of the MPD (long arrow) with the presence of intraductal nodules (short arrows).

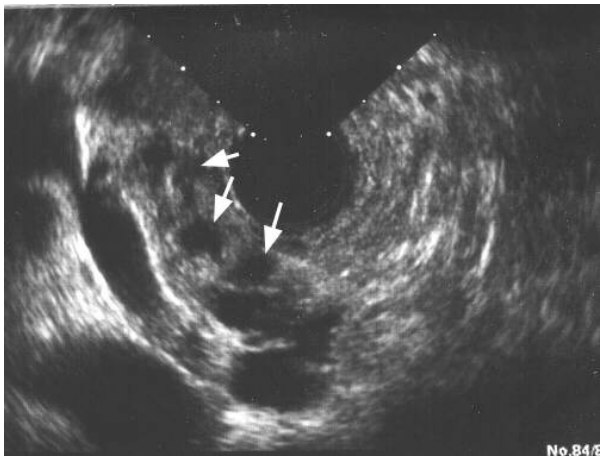

Figure 3. EUS image of multiple cysts (arrows) in BDT-IPMT.

BDT-IPMT (Figure 3). Also, pancreatic parenchymal atrophy is usually noted. There are certain EUS features which suggest malignancy: a main pancreatic duct greater than 10 mm in MDT-IPMT, a cystic lesion greater than 40 mm with irregular, thick septum in BDT-IPMT and mural nodules greater than 10 mm [13].

In a study done to investigate the value of EUS in differentiating malignant from benign IPMT, 51 patients with IPMT were preoperatively examined by EUS. The endosonographic findings were compared with histopathological findings of the resected specimens. MDT-IPMT with MPD dilatation (equal to or greater than 10 mm), BDT-tumors (greater than 40 mm) with irregular septa, and large mural nodules (greater than 10 mm) strongly suggest malignancy on EUS. Thus, EUS was found to be a useful modality for differentiating benign from malignant IPMT [14].

Aithal *et al*. found high sensitivity (86%), specificity (99%), positive predictive value (78%), and negative predictive value (99%) for EUS detection of IPMT. When compared with patients having chronic pancreatitis, the EUS features of dilatation of the pancreatic duct (89% vs. 42%), the presence of cysts (45% vs. 11%), and pancreatic atrophy (32% vs. 3%) were more common, whereas parenchymal features of chronic pancreatitis were less common with IPMT (21% vs. 97%). By multivariate analysis, the presence of no more than one parenchymal feature of chronic pancreatitis suggested a diagnosis of IPMT. It was concluded that EUS may be useful in the initial evaluation of patients suspected of having IPMT. The paucity of parenchymal features of chronic pancreatitis is important in differentiating IPMT from other causes of chronic pancreatitis [15].

Comparative studies found EUS to be more accurate than US, CT and ERCP for diagnosing malignancy in IPMT [13, 16].

EUS-Fine Needle Aspiration

EUS also offers the possibility of EUS-guided fine needle aspiration (FNA) of mural nodules and pancreatic juice from the dilated pancreatic duct for cytology and tumor markers. Pancreatic juice can be sampled for conventional cytological evaluation, and to determine K-*ras* mutation and telomerase activity [2, 17]. EUS-FNA of mural nodules was found to be superior to EUS alone for diagnosing malignancy in IPMT (75% vs. 61%) [18].

In a study by McHenry *et al*., a fluoro-deoxyglucose positron emission tomography (FDG-PET) scan was found to be inaccurate in differentiating benign from malignant cystic lesions of the pancreas; EUS-FNA was more accurate and conferred tissue conformation [19].

In a recent study, investigators evaluated smears of specimens obtained by CT-guided and EUS-guided FNA of the pancreas in 51 cases of mucinous tumors. It was found that IPMT possessed distinctive cytological features which can be used for diagnosis and to distinguish them from other cystic tumors [20].

Another study was conducted to assess the value of analyzing the specimens obtained by EUS-guided FNA and/or biopsy, or the transpapillary biopsy specimens obtained during ERCP for the diagnosis of IPMT and for the detection of malignancy. It was found that the sensitivity of histopathologic analysis of EUS-guided FNA biopsy specimens or transpapillary biopsy specimens was 91% for the positive diagnosis of IPMT with a solid

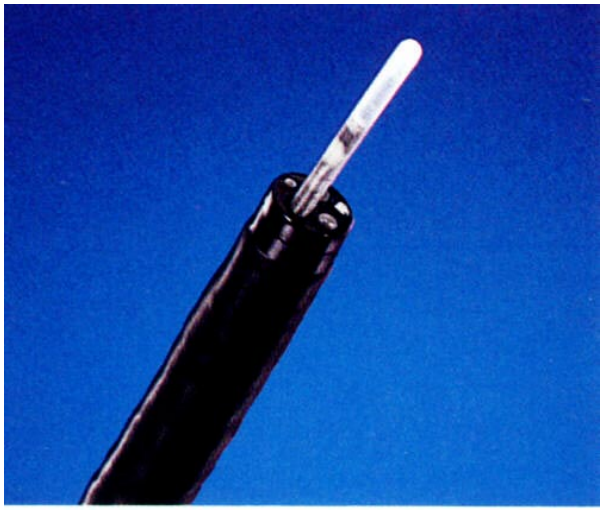

Figure 4. Ultrasound miniprobe introduced through a standard endoscope.

component which is of particular interest as extruding mucus from the papilla was absent in most patients.
Histopathologic analysis of biopsy specimens of malignant IPMT often underestimates tumor grade. The result for cytological analysis of the juice obtained from dilated pancreatic ducts was disappointing [21].
Although EUS-FNA has its limitations, gross and cytological findings can aid in confirming the suspected diagnosis, and integration of complete clinical, sonographic, and cytological information may be the best way to reach the most accurate diagnosis possible [22].
In a safety study, twelve patients with dilated pancreatic ducts underwent EUS-guided duct aspiration. Patients were followed for up to 13 months with no procedure-related complications. This preliminary experience suggests that EUS-guided pancreatic duct aspiration is safe [23].

Intraductal Ultrasonography

Standard echoendoscopes are limited by their large diameter and resultant inability to gain access to ductal systems or stenoses. They are also limited by their relatively low scanning frequencies (7.5/12 MHz), and thus, inadequate image resolution. Ultrasound miniprobes were developed to offer access to narrow intraluminal spaces and to the pancreaticobiliary system. Intraductal ultrasonography (IDUS) is easy to perform and the use of small-caliber, high-frequency catheters offers the advantages of enhanced image resolution and access to strictures. It can be conveniently completed during endoscopic exams and ERCP. The use of IDUS had a significant impact on management (comparable with EUS) in many patients with various gastrointestinal and pancreaticobiliary diseases [24].
The newer models of these probes offer ultraslim diameters, the capability of being inserted over a guidewire, and better acoustic coupling with provision for balloons as a method of maintaining such coupling. The probes used for IDUS can provide high resolution imaging due to the high scanning frequencies used (12-30 MHz). In addition, the small size of the probes used (5-10 F) makes it easy to pass them through the working channel of the endoscope (Figure 4). The probes can be advanced into the MPD under fluoroscopic guidance by free cannulation or over a guidewire.
IDUS has been reported as a reliable method which can be used for a more detailed evaluation of pancreatic tumors especially IPMT (Figures 5 and 6) [25, 26, 27, 28, 29]. The combination of peroral pancreatoscopy with IDUS resulted in the improvement of the differential diagnosis between benign and

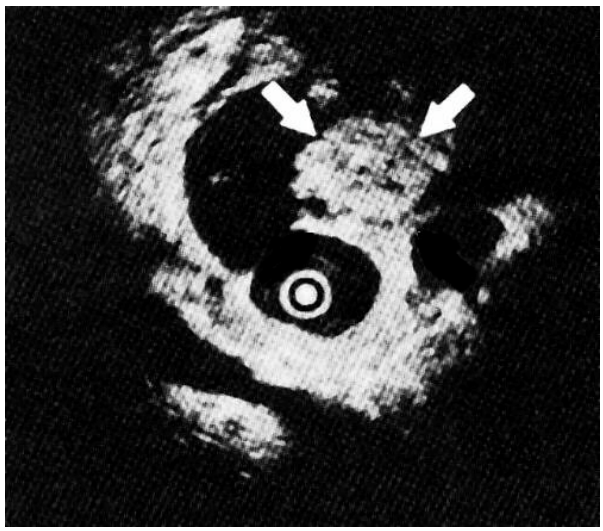

Figure 5. Intraductal papillary tumor with the hyperechoic lesion (arrows) seen protruding into the dilated pancreatic duct.

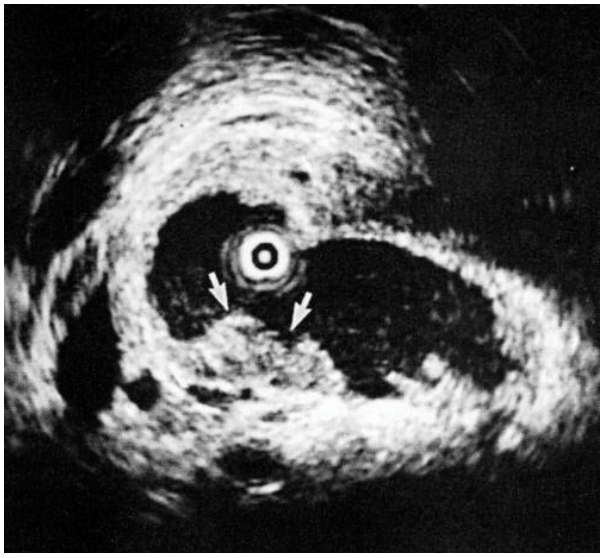

Figure 6. IDUS image of an intraductal papillary tumor revealing a mural nodule (arrows) in the main pancreatic duct.

malignant IPMT and was useful in determining an effective therapeutic approach [30]. IDUS was also found to be useful in preoperative localization and prediction of extension of IPMT, which could prove valuable in selecting pancreatic resection methods [31].

The use of high-frequency (15-30 MHz) ultrasound miniprobes for IDUS permits an accurate diagnosis of tumor extent of MDT-IPMT by virtue of their high resolution. However, there is an inverse relationship between high ultrasound frequency and depth of penetration. Thus, these probes have limited utility in the detection of lesions more than a few millimeters away from the pancreatic duct; moreover, the insertion of the device into the duct is inherently more invasive than standard EUS [25].

US and CT had high specificity, but low sensitivity for the differential diagnosis of neoplastic/nonneoplastic and invasive/non-invasive IPMT. However, EUS and IDUS had high sensitivity and diagnostic accuracy for the differential diagnosis of neoplastic/non-neoplastic lesions. The combination of EUS and IDUS showed a high accuracy rate in the diagnosis of invasive IPMT. Thus, the use of EUS and IDUS contributed significantly to the choice of the treatment for IPMT [32].

3D-Endosonography

Preliminary results have been reported [33, 34] on three-dimensional (3D) IDUS. One-hundred and one patients with various pancreaticobiliary diseases were studied. Three types of images could be produced: dual plane, oblique and surface rendering reconstruction images. Dual plane reconstruction images are useful for assessing tumor extension and its relation to surrounding structures. 3D-IDUS can accurately determine the invasion of pancreaticobiliary cancers into the pancreas/portal vein. Another advantage over conventional IDUS is that the time required for examination is reduced. More time is needed with conventional IDUS to clarify the relationship between lesions and the surrounding organs and vessels.

The clinical utility of virtual pancreatoscopy obtained with 3D-EUS was evaluated in 64 patients with pancreatic diseases including 24 with IPMT. This was done using an electronic radial scanning echoendoscope equipped with software for 3D reconstruction. Virtual pancreatoscopy images clearly displayed the papillary tumors in the pancreatic ducts. Thus, 3D-EUS can visualize the internal structures of the dilated MPD in IPMT. In contrast to pancreatoscopy, virtual pancreatoscopy using 3D-EUS is a non-invasive technique. It may become more useful to diagnose the three dimensional extent and configurations of pancreatic tumors if software and hardware are improved in the future [35].

Conclusion

In summary, EUS is an accurate modality for the diagnosis of IPMT. Certain endosonographic features are highly indicative of a malignancy. The addition of FNA capability further enhances diagnostic capability through sampling of the mural nodules or aspiration of the pancreatic juice for cytology and tumor marker determination. IDUS provides high-resolution imaging of the pancreatic duct and can be used for the

localization and prediction of extension of IPMT. IDUS can be used in conjunction with other modalities (like EUS or pancreatoscopy) to further improve the diagnostic yield. Nevertheless, the exact role of endosonography in distinguishing malignant from benign IPMT remains to be proven. Larger studies evaluating the clinical utility of EUS in IPMT are awaited. Because of the low incidence of IPMT, multicenter trials appear to be the most reasonable methods to prove the efficacy of this new approach.

Keywords Endosonography; Neoplasms, Cystic, Mucinous, and Serous; Pancreatic Neoplasms

Abbreviations BDT: branch duct type; FDG-PET: fluoro-deoxyglucose positron emission tomography; IDUS: intraductal ultrasonography; IPMT: intraductal papillary mucinous tumors; MDT: main duct type; MPD: main pancreatic duct

Correspondence
Assaad M Soweid
Endosonography and Advanced Therapeutic Endoscopy
Division of Gastroenterology
American University of Beirut Medical Center
P.O. BOX 113-6044
HAMRA 1103-2090
Beirut
Lebanon
Phone: 961-1.374.374 ext 5353
Fax: 961-1.370.814
E-mail address: as25@aub.edu.lb

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