Precursor Lesions of Pancreatic Cancer: A Current Appraisal on Diagnosis

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Abstract: The dramatic increase in the number of patients diagnosed with incidental pancreatic cysts through imaging methods provides a unique opportunity to detect and treat these precursor lesions of ductal adenocarcinoma before their manifestation. However, without any reliable biomarkers, the cost-effectiveness and the limited accuracy of high-resolution imaging techniques for diagnose and staging seems troublesome.

Small pancreatic cysts can be easily detected, but many are clinically irrelevant and are not harmful to the patient. Furthermore, patients with clinically benign lesions are at high risk of overtreatment and morbidity and mortality from unnecessary surgical intervention. It is believed that cyst fluid analysis may provide important information for a possible diagnosis, allowing stratification and treatment of these patients. Anyway, only the logical reasoning based on all available information (medical history, imaging, and laboratory analysis of the aspirated cyst fluid) can adequately stratify patients.

It has been considered that there are three precursor lesions of the pancreatic cancer (PC): mucinous cystadenoma (MCA), intraductal papillary mucinous tumor (IPMT) and pancreatic intraepithelial neoplasia (PanIN). MCA and IPMT can be diagnosed by imaging methods, but PanIN are difficult to be identified. They must be detected and treated as soon as possible, as this is the only way to increase survival and reduce mortality of pancreatic ductal adenocarcinoma.

The aim of this work is to establish diagnosis, staging, and the pathological findings and to compare the effectiveness and accuracy of the other imaging methods versus endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) for diagnosis of malignancy in the precursor lesions of pancreatic cancer.

INTRODUCTION

Two hundred and thirty thousand new cases of pancreatic cancer (PC) are reported annually worldwide and 98% die from the disease [1]. In the 60s the 5-year survival rates after diagnosis of PC was less than 4%. Today this rate remains the same despite new treatment modalities [2]. Most important for increase survival rates in patients with PC is the early detection and treatment [3]. However, tumor size makes no difference, because even when PC is less than 1.0 cm it may invades parenchyma, vessels, nerves, and pancreatic ducts smaller than 3 mm. Therefore, the 5 year survival rate of 56% has not improved. It is believed that the identification and treatment of premalignant lesions may be the only way to cure this disease. A great effort has been proposed for early detection and treatment of this type of injury and thus increases the survival rates and quality of life [4].

In the past, pancreatic cystic lesions (PCL) were rarely identified. In recent years its natural history has been better understood, as they have been increasingly identified by imaging methods [5]. As a result many cases of asymptomatic and non-invasive mucinous cystic neoplasms (MCN) are accidentally discovered [6]. It must be underlined that the identification of asymptomatic intraductal papillary mucinous tumor (IPMT) brings the opportunity to cure cancer before it evolving to invasive carcinoma [2]. In the light of current knowledge there are three lesions considered as precursors to PC: mucinous cystadenoma (MCA), IPMT and pancreatic intraepithelial neoplasia (PanIN) [7-9].

RELATIONSHIP BETWEEN PCLs AND INVASIVE PC

Due to difficulties in the differential diagnosis, surgical excision of all cysts, has been recommended routinely in most centers [10-11]. The distinction between benign and malignant lesion is critical, especially when patients have satisfactory clinical

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conditions for pancreatic resection [10]. This procedure exposes patients with benign disease to the high rates of morbidity and mortality associated with pancreatic resections. In addition, due to the increased identification of PCL, a higher number of resections have been performed [11-13]. An important fact is that despite the high risk of malignancy associated with symptomatic cysts, in asymptomatic lesions this possibility can reach 47% cases [14]. These considerations are important because the identification and differentiation between malignant and benign cysts permit to select a group of patients with low chance of malignancy [15]. Therefore, these patients may be followed by imaging without need for more aggressive procedures [6, 16]. Surgical resection of all asymptomatic PCL is expensive and is associated with a high and non-negligible morbidity and mortality, respectively [17]. Despite the complications and the reduced costs when patients are treated in centers of excellence, it is important to weigh the risks and benefits when performing resection of a small and non-invasive IPMT [18]. Resection of all asymptomatic PCL suspected as IPMT is not recommended [2]. Currently

it is recommended that all cases of MPD type IPMT and combined type should be resected when patients are in good clinical condition and have long life expectancy; but when IPMT affects a branch duct (BD) the situation becomes more complicated. In our experience the determinant factors for surgery in asymptomatic patients included: MPD dilatation, cyst size, presence of mural nodules and the results of EUS-FNA. The frequency and period of follow-up in patients with BD type IPMT depends on lesion size. Follow-up period in patients with BD IPMT less than 1.0 cm is annual, 6 to 12 months for those between 1.0 and 2.0 cm and 3-6 months for those larger than 2.0 cm [2, 19].

PRECURSORS LESIONS OF PANCREATIC CARCINOMA

Because in most cases PC is diagnosed in advanced stages, their precursor lesions are difficult to identify [20]. Studies in autopsies showed such precursor lesions [21] In 1999 a new classification was proposed for proliferative lesions affecting pancreatic ducts, and the pancreatic intraepithelial neoplasia
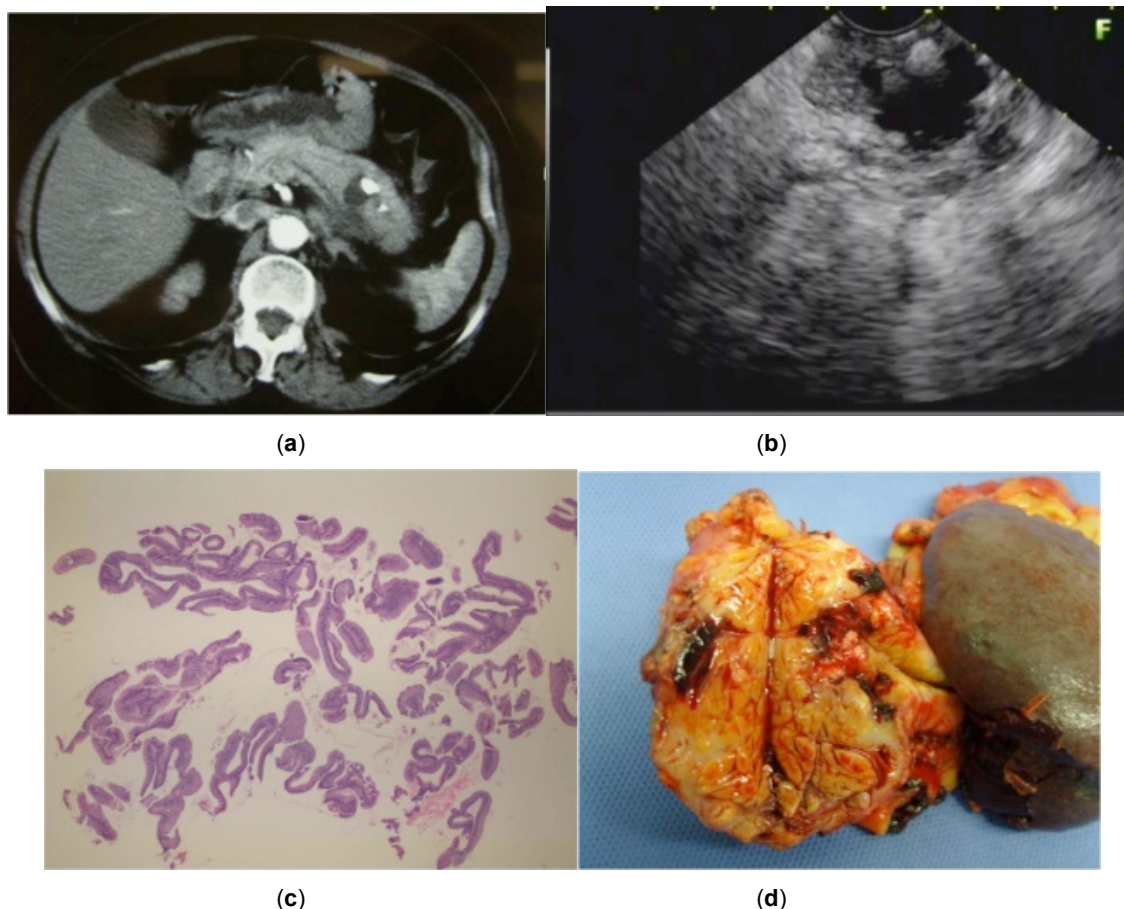

(a) (b) (c) (d)

Figure 1: (**a**) CT showing solid-cystic lesion with calcification in the tail of the pancreas. (**b**) EUS revealed mass in the tail of the pancreas. The FNA showed PanIN type 2 (**c**). (**d**) The pathology of the surgical specimen confirmed the finding of EUS.

(PanIN) was considered as a precursor lesion of PC. Initially it was defined as a lesion originated from small pancreatic ducts measuring less than 5 mm, while IPMT would originate from MPD or BD [22]. However, according to some reports PanIN proliferation may occur in greater caliber ducts including MPD, and this lesion may progress to PC (Figure **1**). Recently this concept has been included in pancreatic cancer oncogenesis [23-24]. PanIN has been found in the periphery of pancreas in patients with PC and their relationship with MCA and IPMT is controversial and difficult to be discussed [25].

The finding of some PanIN in larger ducts has become a major dilemma, because so far there are no clear criteria to differentiate IPMT and PanIN and without a topographic correlation demonstrated by imaging methods it becomes practically impossible [24]. Currently it is suggested that invasive PC originates from noninvasive MCT and PanINs [26]. According to the reviews in the literature PanIN may occurs anywhere in the pancreatic gland, including MPD, BD, interlobular ducts and intercalated ducts [27].

Mucinous Cystic Neoplasm

When MCN communicates with the pancreatic ducts, suggests that it originates from ectopic tissue and according to the current hypothesis it incorporates the ovarian stroma during embryogenesis and the hormone-induced epithelial proliferation give raise to MCA. In turn, a simple epithelial proliferation from MPD and/or BD would originate IPMT. These two types of tumors have common histopathological features such as mucin-producing columnar epithelium, ranging from adenoma to invasive carcinoma. Both are considered pre-malignant or malignant. In general both are associated with good prognosis when compared to PC. However MCA and IPMT differ greatly! The clinical and demographic characteristics of patients are different. Its anatomical characteristics, location, imaging
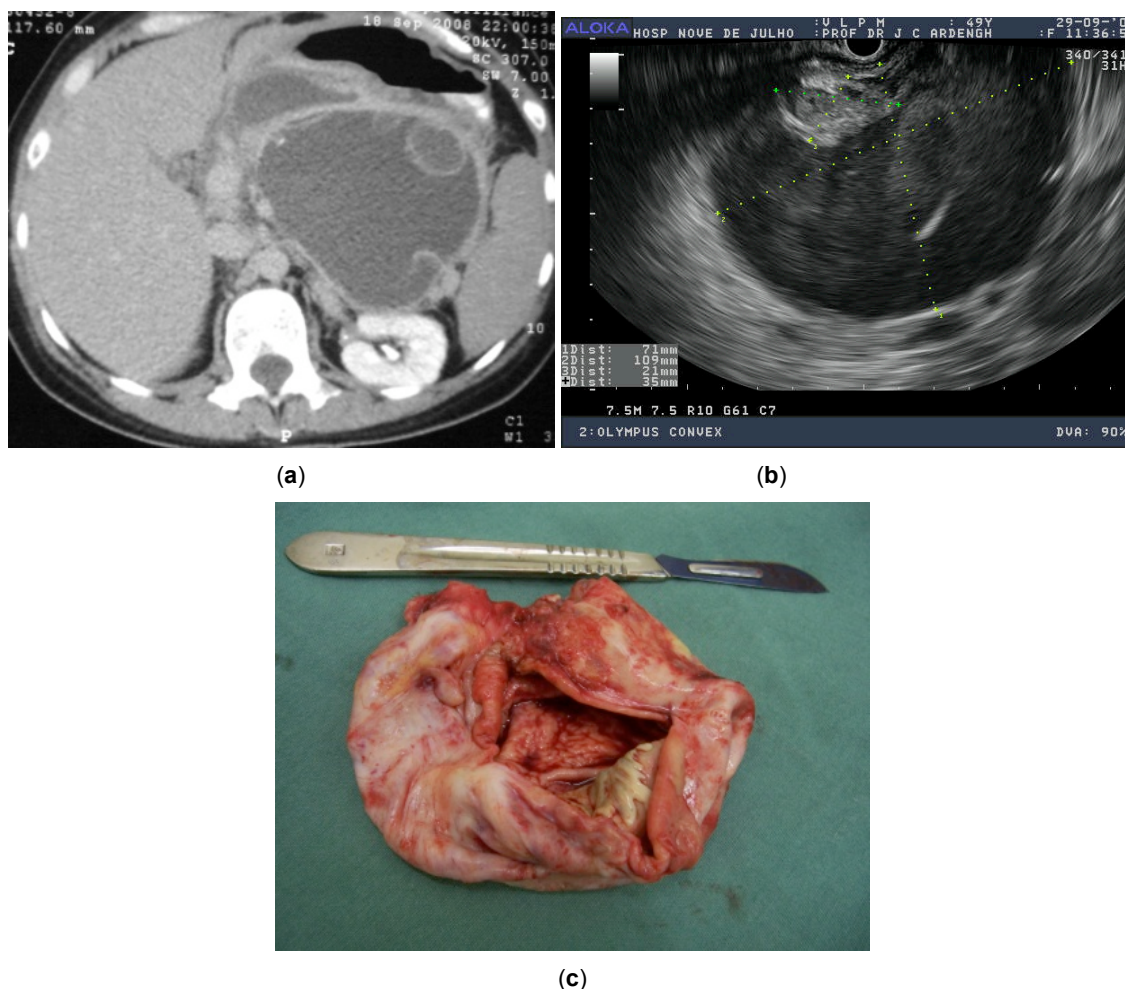

(**a**)

(**b**)

(**c**)

Figure 2: Young patient with an episode of acute pancreatitis. CT shows a cystic lesion compatible with pancreatic pseudocyst (**a**). The EUS findings showed a neoplastic cystic lesion (**b**). Surgical specimen confirmed the mucinous cystadenoma (**c**).

appearance, clinical and pathological stage and prognosis, are also quite different, which justifies the division into two distinct groups [28].

Mucinous Cystadenoma

MCA can be benign or malignant (cystadenocarcinoma) and can be uni-or multilocular and has a fibrous capsule. It comprises neoplastic cells with a gastricoenteropancreatic differentiation associated with an underlying ovarian-type stroma. According to the degree of cytoarchitectural atypia it is classified as adenoma, carcinoma "*in situ*", or invasive carcinoma. They seem rare, but in clinical practice this is not the case (Figure **2**) [10, 15].

Cystadenocarcinoma can present nodules, masses or vegetations attached to the cyst wall [16]. Occurs almost exclusively in women and the vast majority of tumors are located in the body and tail of the pancreas (Figure **3**) [24].

Intraductal Papillary Mucinous Tumor

IPMT is characterized by dilatation of main pancreatic duct (MPD), branch duct (BD) or both (BD + MPD), and is filled with mucous secretion. The first type is known as IPMT type 1, and that affecting only BD is known as IPMT type 2, and type 3 is mixed. Multiple dilated BDs can coalesce and mimic a MCA (Figure **4**) [10, 15]. Occur more frequently in men and in head of the pancreas (Figure **5**) [29]. IPMT is an intraductal tumor, formed by papillary proliferation of mucin-producing epithelial cells, which can exhibit gastric, intestinal and biliopancreatic differentiation. This tumor presents different pathophysiological features, including: diffuse and scattered polypoid lesions, within a dilated MPD [28-29].
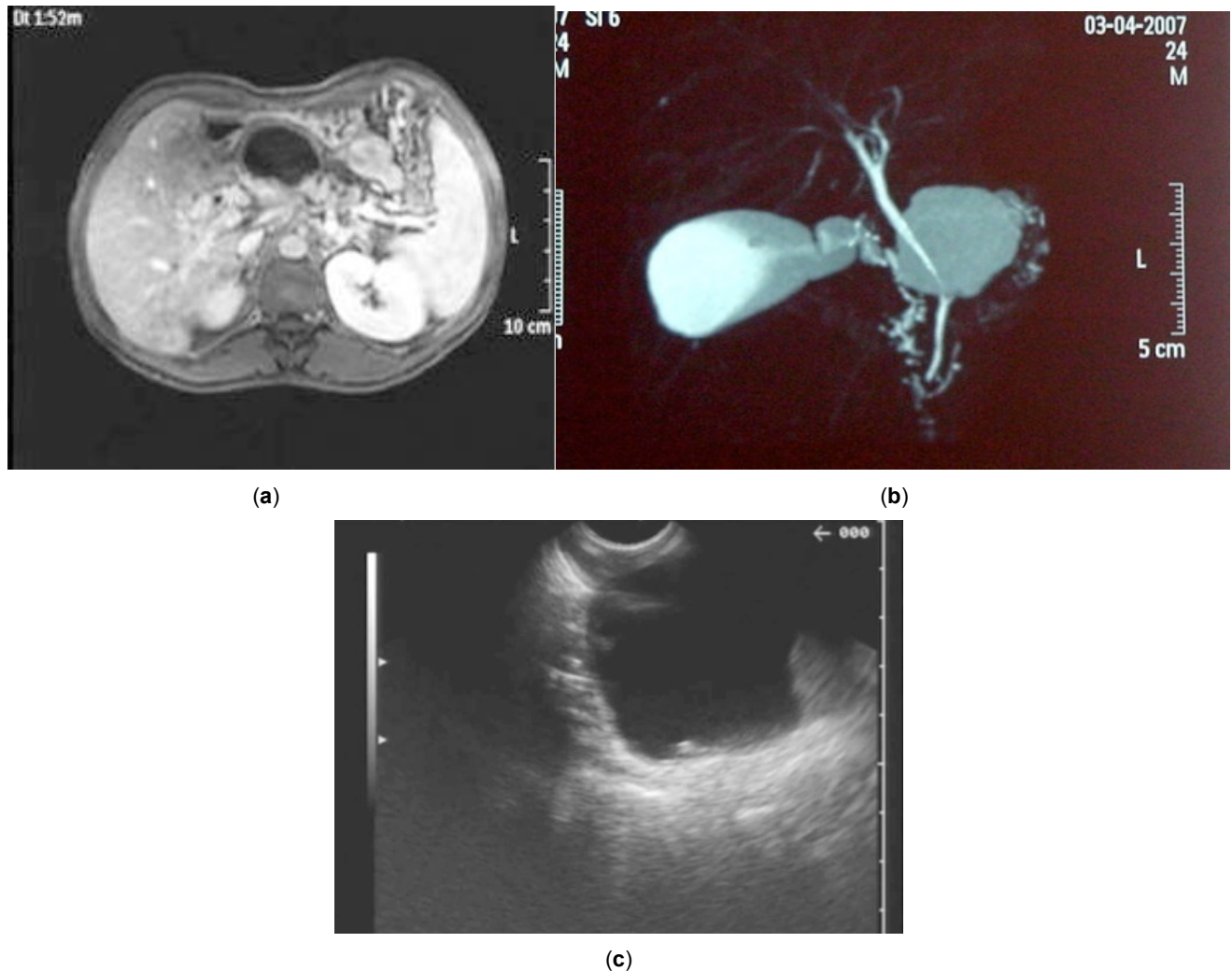

(**a**)   (**b**)

(**c**)

Figure 3: Asymptomatic patient during checkup examination a pancreatic cystic lesion was identified (**a**). MRI/MRCP confirmed the presence of a PCL with communication with MPD (**b**). EUS showed vegetation inside and the final diagnosis was cystadenocarcinoma inoperable.
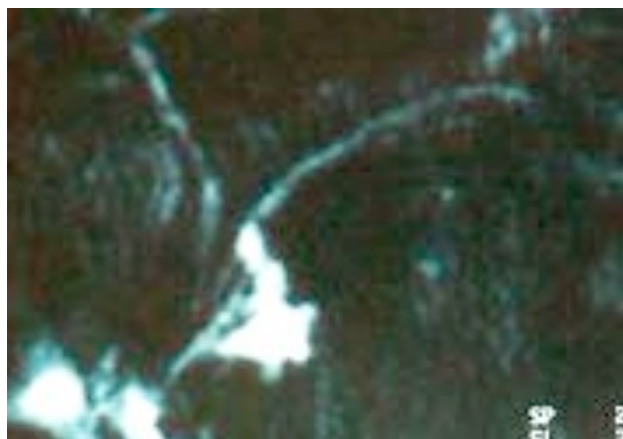
Figure 4: Multiple dilated BDs mimicking a MCA.

IPMT should be considered a distinct disease from PC and PanIN [29]. Since the studies from Ohhashi *et al.* the term carcinoma "*in situ*" has been used for IPMT with severe citonuclear atypia without invasive carcinoma [30]. There are numerous reported cases of "*in situ*" pancreatic cancer and most are considered as IPMT [31-32].

Pancreatic Intraepithelial Neoplasia (PanIN)

The history of pancreatic epithelial lesions dates back to 1924 when Nakamura described the duct epithelial hyperplasia of pancreatic epithelium. The postmortem examination in 114 patients with PC identified four cases of papillary hyperplastic transitional epithelium in the periphery of the organ, and foci of carcinoma "*in situ*" were present away from the central focus of PC [33]. These authors reported that hyperplasia of papillary or adenomatous type was often found in pancreas with PC compared to pancreas without this injury (control group). Since then it is believed that those proliferative lesions progresses to PC. The occurrence of ductal papillary hyperplasia was three times higher in patients with PC than in control cases. Evident atypia and carcinoma "*in situ*" occurred in 20% and 18% respectively in pancreas with PC and none of these findings was found in controls. The authors mentioned that atypia and carcinoma "*in situ*" were the precursor lesions of PC [34]. Another study found atypical hyperplasia in 29.2% of pancreas with PC and in 0.7% of pancreas without PC. In this series
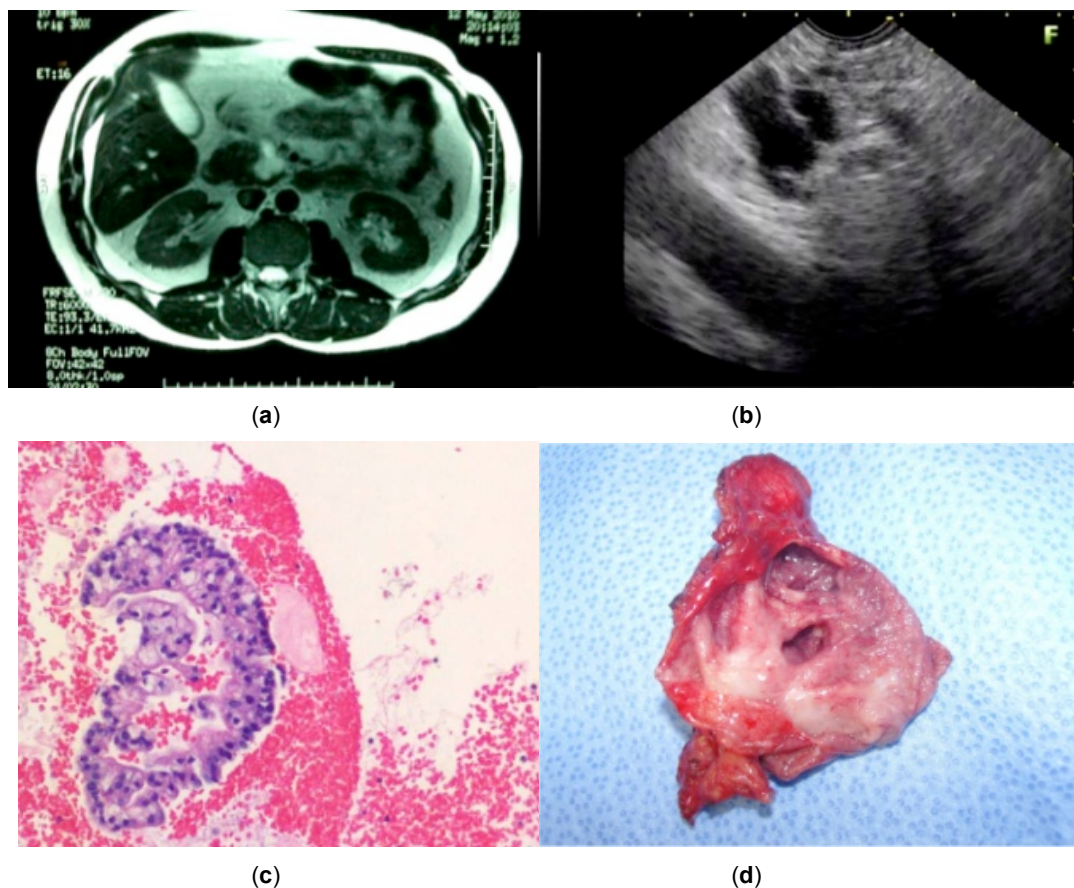

(a)   (b)

(c)   (d)

Figure 5: Male, with one episode of acute pancreatitis. MRI/MRCP show PCL in head of the pancreas (**a**). EUS shows a IPMT localized in the uncinate process (**b**). FNA = IPMT *in situ* carcinoma (**c**) and the uncinectomy confirmed the findings of EUS-FNA (**d**).

of cases the incidence of PC was 2.0%, atypical hyperplasia 1.1%, papillary hyperplasia, 6.6% and non-papillary hyperplasia, 18.1% [21].

According to initial definition PanIN does not involve MPD and is generally so small that could not be identified by conventional imaging techniques [22]. However, PanIN originates from BDs or even from smaller ductules (<5mm), extends to proximal MPD, and can be identified by brushing or samples obtained during endoscopic retrograde cholangiopancreatography (ERCP) [29]. PanIN is usually found in the periphery of the gland with PC but can be found in pancreas without PC. For this reason this finding raises the hypothesis that PC originates from normal epithelium [22].

CLINICOPATHOLOGIC FINDINGS MUCINOUS CYSTADENOMA

MCA affects almost exclusively women between 5th and 6th decades of life. Patients with large tumors may present vague abdominal pain and discomfort. Anorexia and weight loss may indicate malignancy. Peripheral calcifications may be present. It affects the head, body and tail in 10%, 70% and 90% of cases, respectively. It's solitary, ranges from 6 to 35 cm, and is composed of multiple loci and a fibrous wall. It has no communication with MPD [10-11].

Despite recent Japanese report giving emphasis to microscopic communications between tumor and MPD [35]. The occurrence of peripheral calcification, wall thickening, vegetations, nodules, elevations, vascular involvement and peripheral hypervascularization suggest the diagnosis of CAC. According to WHO MCA is classified into three categories (based on the degree of dysplasia): benign, borderline and malignant. The degree of atypia is classified according to the most advanced degree of atypia ranging from dysplasia to carcinoma [20]. This tumor may present ovarian stroma, and estrogen and progesterone receptors. For many authors only cystic tumors which contain ovarian stroma can be classified as MCA. The fluid inside the cyst is often viscous and clear [10, 15]. MCA is a neoplasm composed of mucin-producing cells [36].

Current clinical, pathological and molecular observations, established that mild dysplasia within MCA progresses to moderate dysplasia and then to carcinoma "*in situ*". It seems clear that if left untreated carcinoma "*in situ*" rising from MCA epithelium can progresses to invasive carcinoma. These reports support the hypothesis that noninvasive MCA evolves to invasive carcinoma in some years and its clinical implications are evident [37].

Intraductal Papillary Mucinous Tumor

Patients with IPMT may complain of pain, often in the epigastric region, radiating to the back [38]. The overproduction of mucin leads to MPD obstruction and can explain the pain exacerbated by food intake. Other signs and symptoms described include weight loss, fever and jaundice [39]. Many patients are previously diagnosed as chronic pancreatitis, due to changes in MPD (Figure **6**). Several factors can predict malignancy: involvement of MPD, size, mucin leaking from the papilla Figure **7**, jaundice and diabetes [40-41]. Previous reports showed that IPMT up to 30 mm
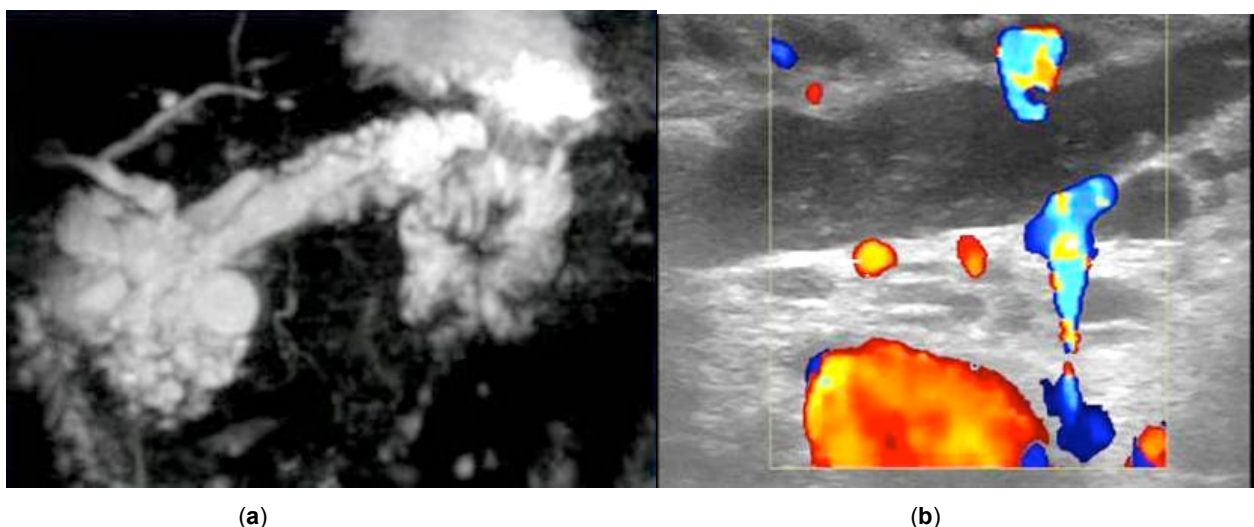

(**a**)   (**b**)

Figure 6: Man, 65 y-old (malignant IPMT). (**a**) Treated for chronic pancreatitis (8 years). During treatment developed jaundice. Total pancreatectomy was performed. (**b**) Intraoperative US revealed dilated MPD and mass in the pancreatic head.
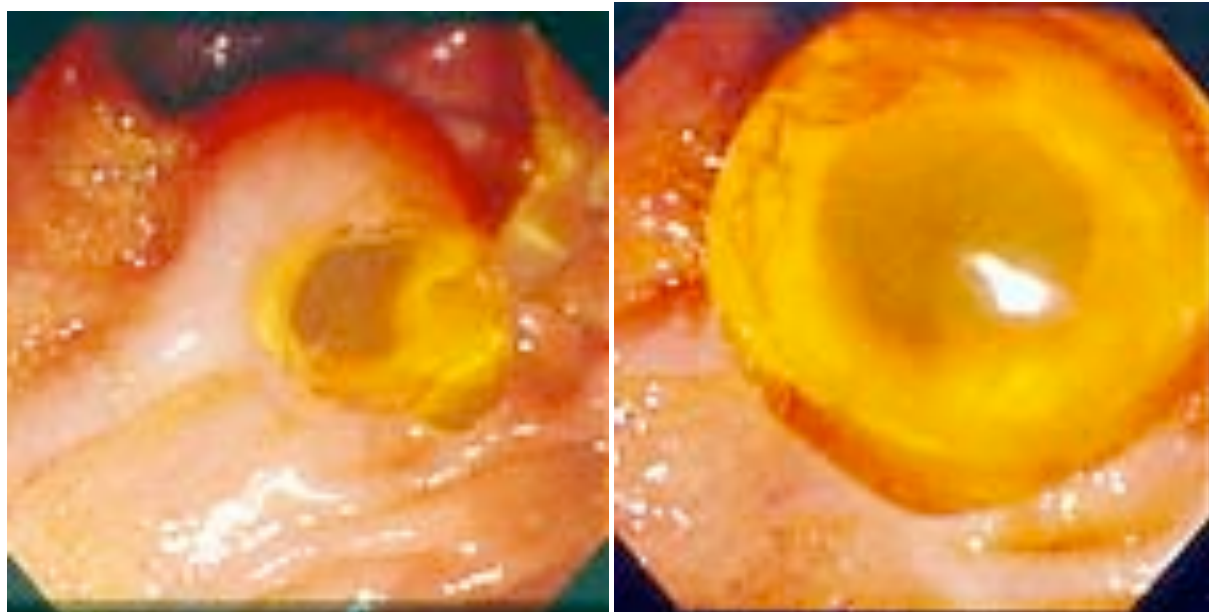
Figure 7: Typical endoscopic image of "fisheye" in invasive IPMT.

were all benign and tumor sizes between 1 and 30 mm, and mural nodules were associated with high rates of malignancy [25, 42-43].

IPMT occurs in both men and women. There is a slight tendency to occur in men and in the 8th and 9th decades of life. Often these patients experience episodes of acute pancreatitis (AP) or elevation of amylase. The details about the disease progression and invasion are not clear and even established. It is estimated that the average time for development of malignancy varies between 5-7 years after diagnosis [38, 44]. Generally, IPMT size ranges from 1.0 to 2, 0 cm. The rate of progression from benign to malignant is unclear. The preferred location of IPMT is the pancreatic head, especially in uncinate process (Figure **5**) [10-11, 35]. Tumor affecting BD occurs in young individuals and its malignant potential is lower compared to MPD type or mixed type [19]. Therefore, tumor shape must be identified and must be accurately measured, because the clinical course is quite different from that observed in MPD and mixed type [45]. The degree of epithelial dysplasia may be classified as: mild, moderate and severe, and a focus of superficial or early carcinoma are evident when MPD shows elevations and/or nodules [8, 45]. A malignant tumor originating from IPMT presents an exuberant papillary component when compared to malignant tumors originated from MPD [46-47]. This tumor consists of mucin-producing cells disposed in papillary arrangements, leading to intraductal wall thickening. Histologically IPMT is classified in the same way as

MCA. Approximately one third are associated with invasive carcinoma [2]. Clinical differentiation between noninvasive IPMT and invasive PC is difficult. Furthermore, detection of this association is the most important prognostic factor in patients with IPMT. Importantly, similar to MCA, IPMT may show a focal invasive carcinoma which has a favorable behavior and this diagnosis cannot be established by biopsy alone but is based on histopathological examination of the surgical specimen [8].

In half of IPMTs associated with invasive carcinoma the histologic type is the colloid or muconodular and the other half are ductal (tubular) [2, 35]. This distinction is critical to determining prognosis, as IPMT associated with colloid or muconodular carcinoma has a better prognosis than when associated with ductal type [48-49]. While there is a tendency to imagine that IPMT is a uniform illness, morphological and immunohistochemical studies have defined several subtypes [50]. This disease has been classified according to the type of duct involvement and based on the microscopic level of differentiation of neoplastic cells. Follow-up (41 months) of patients with BD IPMT and MPD IPMT, revealed increased diameter in 1 case (2%) of BD IPMT compared with 4 cases of MPD IPMT(51). Morphological assessment of IPMT epithelium has important clinical significance [2]. Intestinal type IPMT is associated with invasive carcinoma, both colloid or muconodular type [48]. Biliopancreatic type is associated with ductal PC [35, 48]. It is important to distinguish these associations

because muconodular or colloid carcinoma has a better prognosis as compared to PC [48].

Prognosis of patients with noninvasive IPMT is better when compared to invasive carcinoma, so it is interesting to establish criteria for individually identifying these two entities [49]. Studies suggest that the progression from benign to invasive IPMT can be detected by imaging follow-up, for example, transabdominal US [2].

Increases in MPD diameter by 2.2 mm/year, the cyst diameter by 11.3 mm/year, development or increasing in mural nodule size larger than 3.3 mm / year are predictors of diagnostic accuracy for invasive IPMT [52]. These parameters are sufficient to indicate surgery in these cases [2].

Pancreatic Intraepithelial Neoplasia (PanIN)

The clinical and pathological aspects of PanIN are not accurate because there are few reported cases. However, the main objective is to identify PanIN as precursor of PC, as the term PanIN was created in an attempt to rationally explain the progression from hyperplastic epithelium to PC. The literature describes six cases and demonstrates that a clear progression occurred from PanIN to PC [53-55]. Among them, four patients underwent pancreatectomy and showed multifocal lesions represented by PanIN-3 associated with chronic pancreatitis (CP). After the initial pancreatectomy PC developed in the remnant pancreas between 17 months and 29 years after surgery. The other two patients underwent pancreatectomy for PC. In one, an extensive atypical papillary hyperplasia was observed in the resected surgical margin. PC developed in the remaining pancreas with liver metastases 9 years after surgery. The latter had PanIN-3 and showed progression to PC three years after surgery. Another case was represented by a small cystic lesion communicating with MPD and was identified by endoscopic ultrasound (EUS) whose fine needle aspiration (FNA) showed atypical cells and mucin. The distal pancreatectomy specimen showed adenomatous type IPMT of 0.8 cm, with multiple foci of PanIN 1 and 2 associated with CP and pancreatic atrophy [2].

Noninvasive PanIN progression to invasive PC suggests a unique opportunity to treat and cure PC before it progress to an incurable disease. The biggest challenge has been to characterize it by means of imaging, because PanIN is too small to be detected by current imaging methods. A recent morphological study of specimens resected from pancreas of families with a history of PC revealed that this challenge can be overcome and that PanIN may be detected and present clinically relevant lesions [56]. This study examined the changes in pancreatic parenchyma associated with PanIN in eight specimens of surgically resected pancreas. These pancreatic resections have been done as part of a follow-up study of individuals with family history of PC. Surgery was performed early before PC development and infiltration. It is indisputable that even PanIN associated with mild dysplasia showed lobular and parenchymal atrophy. The parenchymal and lobular atrophy was directly correlated with the findings of CP by EUS. These findings have two important clinical implications: a) suggests that PanIN can be detected by current imaging methods and b) it may cause minor changes in patients with family history of PC thus revealing the existence of precursors to invasive PC [56]. Foci of parenchymal atrophy associated with PanIN lesions may be seen in elderly patients with no family history of invasive PC [57]. Localized parenchymal fibrosis may be associated with PanIN 3 [24]. In this case fibrosis appeared in a check-up examination as a hypoechoic area in the head/body transition region of the pancreas. The patient underwent central pancreatectomy. PanIN involving MPD and BD, was identified in the surgical specimen. The authors noted that PanIN can cause BD obstruction and focal fibrosis was confined to a single lobule draining into the obstructed BD [57].

Relationship Between IPMT and PanIN

IPMT arises from MPD or BD while PanIN arises from BD or even from lower ramifications, according to its initial definition [22]. According to this definition, one of the differences between IPMT and PanIN is the duct size containing a lesion [24]. At least hypothetically IPMT would originate from more proximal ducts with a tendency to spread by the distal ducts, because its walls are more fibrous, firm and thick. There appear to be other factors involved in tumor invasion and not only the thickness of duct wall. IPMT is generally characterized by mucin hypersecretion and may be distinguished from PanIN. However, intraductal papillary tumor without mucin, an old term for IPMT is encompassed by this term and the differential diagnosis between PanIN becomes problematic. For example, a small papillary lesion originally described as PanIN has been spread in a more proximal direction, along a small diameter duct (BD), with eventual dilatation. In this case it could be diagnosed as IPMT. Thus, when IPMT is small and has no mucin secretion,

it is impossible to distinguish morphologically these two entities [24]. Thus isolated dilatation of BD, arguably identified by imaging methods, may be consider as a morphological imaging finding of PanIN when the presence of mucin cannot be confirmed. From a morphological point of view there are many similarities between PanIN and IPMT: columnar mucin-producing cells arranged in a flat shape, some produce mucin and may show atypia and other cytoarchitectural changes [27]. Importantly, IPMT is a neoplasm detected by imaging and produces large amounts of mucin, while PanIN is a microscopic lesion without mucin hypersecretion [4]. This description is fundamental to explain the detection of minimal dilations of BD by MRI/MRCP and EUS with or without mucin production. Sometimes these PCL detected by MRI are erroneously labeled as IPMT due to BD dilation. It is also noteworthy that dilation of BD may be caused by obstruction of its proximal portion containing PanIN or even by mucin hypersecretion as PanIN located in BD can secrete mucin itself.

IMAGING METHODS

Transabdominal Ultrasound (US), Computerized Tomography (CT) and Magnetic Resonance Cholangiopancreatography Imaging (MRI / MRCP)

US has no good results. CT is the primary imaging method for diagnosis of PCL [58]. The presence of unilocular or macrocyst favors the diagnosis of MCA. Although rare, peripheral calcifications are specific for the diagnosis of MCA [59]. IPMT involves MPD and/or its side branches. CT is excellent for detecting IPMT. In this context a study showed US has lower diagnostic sensitivity when compared to CT (Figure **8**). The sensitivity of US was 17.3% and CT was 51.6%. US contributed to the detection of IPMT up to 35.7% of cases [28]. Echographic characteristics found by US and EUS are similar: MPD and BD dilatation MPD, ducts filled with mucus, hiperecogenicity of duct wall and hypoechoic and hyperechoic mural nodules [16, 28]. CT scan of MAC shows an oval encapsulated lesion, with micro or macrocyst inside, with unilocular cyst being observed in a small number of patients. The detection of nodules or vegetation inside the cyst is correlated with malignancy. Tiny cysts may occur in the wall of MCA and are sometimes diagnosed as mural nodules [28]. These characteristics can be clearly demonstrated by MRCP [60]. Communication between a PCL and the MPD is less common, but this finding does not make a definite diagnosis of MCN [25, 28, 60]. The information provided by CT, MRI and EUS

(detection of multiple septa within the cysts and nodules adhered to the cyst wall) can make the differential diagnosis between MCA and a pancreatic pseudocyst (PPC) [11, 16]. MRI shows MPD dilation, and is better to detect intramural nodules and their connection to MPD, than Endoscopic Retrograde Cholangiopancreatography (ERCP). Despite the excellent images obtained by CT and MRI they do not exhibit high diagnostic accuracy in determining the presence of malignancy [60].

Figure 8: Man 86 y-old with an increase of head of the pancreas identified by CT (malignant IPMT).

ENDOSCOPIC ULTRASOUND (EUS)-GUIDED FINE NEEDLE ASPIRATION (FNA)

EUS can be used to evaluate pancreas and detailing the cystic lesions. They are anechoic, filled with fluid and contrast with pancreatic parenchyma, which is hyperechoic [16]. The detailed image obtained by EUS provides morphological criteria to differentiate the various types of cysts [61]. EUS-FNA has been used for histologic diagnosis of IPMT. It has a high accuracy, security besides being a painless method for obtaining material for histologic diagnosis of such tumors [62]. The sensitivity, specificity and PPV, and PNV were 28%, 100%, 100% and 18% respectively in a series of 95 patients [63]. However, another study showed better results of EUS-FNA in the diagnosis of IPMT with sensitivity, specificity, PPV, PNV and accuracy of 82%, 100%, 100%, 92% and 94% respectively [64].

Cytological analysis of the cyst contents should evaluate the presence of columnar epithelial cells and mucin. Epithelial cells are present in 48% and represent a highly diagnostic finding [65]. Moreover,

the presence of mucin suggests the diagnosis of MCA. Malignant epithelial cells can be seen, particularly when nodules are observed within the cyst [66]. Precautions must be taken to prevent contamination of the cystic contents with gastric or duodenal mucosa. When these epithelial cells (high digestive tract) are found in the cyst contents may be confused with those found in MCA.

The cytological analysis of the material aspirated from a dilated MPD or from a cyst associated with IPMT shows similar aspects compared to MCA: malignant or benign columnar epithelial cells, usually associated with large amounts of mucin (Figure **9**). The cystic content is a rich source of tumor markers. Huge amounts of glycoprotein secreted by the dysplastic epithelium can be examined and provide various diagnoses. The presence of extracellular mucin found in aspirated pancreatic cystic fluid has moderate predictive value for diagnosis of MCA [67]. Some studies suggest that carcinoembryonic antigen (CEA) or CA 72-4 are effective for the diagnosis of MCA [16, 68]. These carbohydrate antigens are secreted by the MCA epithelium and are present in high concentrations; these two markers are found in very low levels in serous cystadenoma (SCA). Although the discrepant levels found in mucinous and non-mucinous cysts, CEA is the best marker for differential diagnosis [69]. CEA less than 5 ng / ml is strongly suggestive of SCA and values exceeding 800 ng / ml is predictive of MCN [69]. Recent studies have demonstrated that K-ras mutation of suppressor genes and telomerase activity are found frequently in mucinous cystic lesions [70]. CA19-9 is encountered in the fluid of pancreatic cysts and has been used as a marker, but it has proved to be less sensitive and specific for diagnosing these tumors [16, 69].
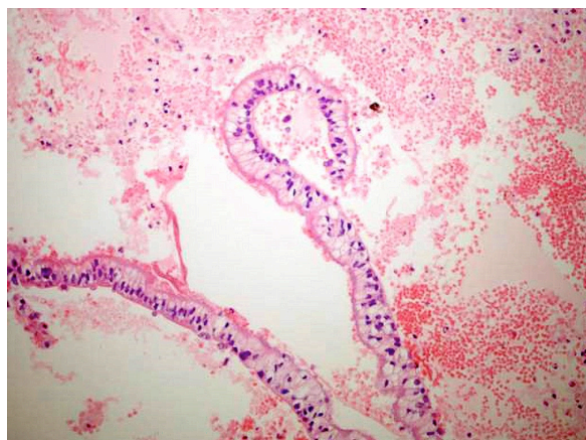

Figure 9: Microhystology. Low-grade of mucinous cystic neoplasm.

CONCLUSIONS

The diagnosis of PC in the early or initial stage is difficult to do! Perhaps not too far it will be possible if we can imagine that science has evolved rapidly, allowing the introduction of new molecular biomarkers, and due to the emergence of new techniques for detailed analysis of cystic contents. MCNs should be identified early, therefore, every effort must be made. Perhaps a better understanding of the natural history of PCL would enable to find the missing link between a potential cystic precursor lesion and its progression to pancreatic cancer.

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