

## **PRE-INVASIVE DUCTAL NEOPLASIA OF THE PANCREAS**

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The most important developments in pancreatic tumor pathology in the past few years have taken place in the area of preinvasive ductal neoplasia. In the ensuing text, an overview of these neoplasia is provided.

### **Pancreatic Intraepithelial Neoplasia (PanIN)**

It has been speculated for more than half a century that the development of invasive ductal carcinoma from normal pancreatic ducts is preceded by an intraductal neoplastic transformation in the ducts. These intraductal proliferative changes have been referred to by various names including hyperplasia, atypical hyperplasia, dysplasia among others.

In 1999, a group of pathologists were brought together by the NCI in Park City, Utah, in a think-tank meeting, to discuss precancerous ductal lesions. At this meeting, pancreatic intraepithelial neoplasm (abbreviated as PanIN) was adopted as the name for these lesions, and these lesions were proposed to be divided into four grades. The criteria were published in *Am J Surg Path* 25(5): 579-86, 2001<sup>1</sup>.

#### *PanIN- Criteria and grading<sup>1</sup>*

Those intraductal lesions composed of tall columnar cells without any atypia or papilla formation (previously called mucinous hypertrophy) were included into the neoplastic category as PanIN-1A/ mucinous duct lesion, because they often harbor some of the earlier molecular alterations attributed to carcinogenesis. Those that have minimal/no atypia but show early mucosal foldings are graded as 1B. Lesions with substantial pseudostratification of the cells and some degree of cytologic atypia are graded as 2. When there is irregular papillary architecture, with tufting, cytologic atypia, necrosis, mitoses and loss of polarity of cells, it is regarded as PanIN-3 (CIS).

PanINs show molecular alterations associated with neoplastic transformation<sup>10</sup>. In fact, this was the main reason why mucinous duct lesions, which were previously termed as mucinous hypertrophy/metaplasia were included in the PanIN spectrum. There is a progressive accumulation of molecular alterations from PanIN1- to invasive carcinoma. Some alterations such as k-ras mutation are early events, whereas others such as p53 loss take place later in the spectrum.

Early PanINs are common incidental findings. The frequency of PanINs in different diagnostic groups (normal/non-neoplastic pancreata, secondary tumors, CP-chronic pancreatitis, and DA-ductal adenocarcinoma) in the Wayne State University database was documented in a recent publication by Andea et al, (*Mod Pathol*, 16(10), 996-1006, 2003)<sup>11</sup>. In that study, PanINs were identified even in normal pancreata (20%) but were significantly more common in patients with ductal adenocarcinoma (80%). However, higher grade PanINs, especially PanIN-3, were seldom seen in pancreata without invasive ductal adenocarcinoma, and most of the PanINs that were seen in pancreata without invasive ductal carcinoma were PanIN-1.

### **Association of PanINs with carcinoma**

There is evidence (some circumstantial) that support the association of PanINs with invasive carcinoma. As in other exocrine organs such as breast and prostate, it is expected that the precursor of invasive ductal carcinoma lie within the ducts. There are morphologic, molecular and genetic similarities between PanINs and invasive carcinomas. PanIN-3 is more commonly seen with invasive cancer. There are some patients with PanIN-3 who developed invasive carcinoma during follow up.

### **Reporting of PanINs in surgical pathology**

It should be understood and conveyed to the clinicians that, the word neoplasm has been applied to PanINs to reflect the clonal nature of these lesions and that they express cancer associated genes. That is not to say that they require clinical treatment. In fact, PanINs 1 and 2 are common incidental findings<sup>11</sup> and generally not reported. PanIN 3, on the other hand, is strongly suspected to be a significant process (that may require therapy); however, there is not enough evidence to prove this point yet.

### **Mass Forming Pre-Invasive Neoplasia**

In addition to the PanINs, which are microscopic, incidental forms of dysplasia, there is another group of *pre-invasive* neoplasia that typically forms clinically detectable masses<sup>12</sup>. In contrast with the microscopic/incidental nature of PanINs, these mass-forming preinvasive neoplasia are characterized by either large papillary tumors that are non-invasive or cystic masses. Intraductal papillary mucinous neoplasms, intraductal oncocytic papillary mucinous neoplasms and mucinous cystic neoplasms are the tumor types that can be placed in this category of mass-forming pre-invasive neoplasia.

### **Intraductal papillary mucinous neoplasms (IPMN)**<sup>13-16</sup>

The most important category of mass-forming preinvasive neoplasia is intraductal papillary mucinous neoplasms (IPMNs). IPMN as an entity was first recognized by Ohashi et al. in their report of four cases of mucin-producing tumor of the pancreas.

In the 80's and early 90's, these tumors were reported under various names that can be placed into three broad categories: 1. Because of the exuberant papilla

formation in some cases, the terms *papillary/villous adenoma/neoplasm/carcinoma* have been used in some series. Some authors have referred to IPMNs as mucin producing tumors, because the neoplastic cells are mucinous and secrete abundant mucin into the lumen of the cystically dilated ducts. Because these tumors are *intraductal* and communicate with the main ducts, the mucin produced exudes from the ampulla of Vater, a characteristic endoscopic finding that has led to the name “*mucin producing tumor*”. In some examples of IPMNs, the ductal dilatation is very prominent, leading to multilocular cyst formation, resembling mucinous cystic neoplasms, hence the name *ductectatic variant of mucinous cystic tumor, or mucinous duct ectasia*.

There is a spectrum of cyst and papilla formation in IPMNs. In some cases, the pancreatic duct becomes tortuous and shows irregular dilatation. In other examples of IPMNs the ducts are filled with tan friable papillary nodules, with no significant “cyst” formation.

There is a spectrum of cytoarchitectural atypia in IPMNs ranging from adenoma to CIS. Foci with simple columnar cells, abundant apical mucin and well-polarized nuclei without any cytologic or architectural atypia are regarded as adenoma. Those that have substantial disorganization, loss of polarity, nuclear enlargement and pleomorphism are classified as CIS. There is a spectrum of changes in between that is regarded as borderline.

#### Different patterns of papillae in IPMNs

There are different patterns of papillae in IPMNs. Most look like villous adenomas of the colon, with pseudostratified columnar cells. We refer to this as the intestinal pattern, which typically expresses intestinal differentiation markers MUC2 and CDX2. In some, papilla are more complex and lined by cuboidal cells reminiscent of biliary papillomatosis, thus we refer to as pancreatobiliary. Other papillae resemble gastric foveolar epithelium.

IPMNs are associated with invasive carcinoma in 30% of the cases. Two types of invasive carcinoma are seen in IPMNs. The tubular type is morphologically identical to conventional ductal adenocarcinoma, and the colloid type is characterized by mucin lakes that contain scanty, detached carcinoma cells. The 5-yr survival rate of resected conventional ductal adenocarcinoma is less than <10%; whereas, that of colloid carcinoma (with or without IPMN) is >55%<sup>4</sup>.

MUC1 and MUC2 expression profiles of tubular and colloid carcinomas are the mirror image of each other<sup>12</sup>. The vast majority of tubular carcinomas expresses MUC1 and lack MUC2; however, all colloid carcinomas are positive for MUC2 and negative for MUC1.

Emerging evidence<sup>12</sup> suggests that there is a dichotomy in pancreatic ductal carcinogenesis: MUC1 is the marker of the pancreatobiliary pathway (PanINs and pancreatobiliary pattern of IPMNs) that leads to conventional ductal adenocarcinoma, whereas MUC2/CDX2 is of the intestinal pathway which is associated with the colloid type of invasive carcinoma and indolent behavior.

### **Clinical significance and prognosis of IPMNs**

The factors that make IPMNs a clinically significant category are the following. IPMNs form relatively large tumors (mean size= 4.5 cm) in the pancreas, and produce various symptoms and signs including functional compromise of the organ. Of note, a third of the patients with IPMNs have other malignancies (in other organs). It is not known whether this is coincidental since these patients are older (mean age=68) or whether IPMNs are a part of senescence-related propensity for tumorigenesis. More importantly, in >30% of the cases, IPMNs are associated with an invasive component. Although the “overall” 5-yr survival of IPMNs is 70% (incomparably better than that of ordinary ductal adenocarcinoma which is <10%), this statistic includes all adenomas, CIS and invasive carcinomas. In general, those with adenoma have very good prognosis, but those with invasive carcinoma may have an aggressive clinical course.

Some histologically non-malignant examples of IPMNs (without any in-situ or invasive carcinoma) followed an aggressive clinical course<sup>16</sup>. This has led to the speculation that the IPMNs are unpredictable. Other potential reasons for this discordance include multifocal nature of these tumors and focality of carcinoma, which can be missed both surgically and grossly. In addition, some cases of IPMNs were associated with invasive carcinoma elsewhere in the organ, away from the IPMN, suggesting that IPMNs may also be markers of invasive carcinoma in addition to precursors.

Another peculiar observation about IPMNs is that even tubular-type invasive carcinomas arising from IPMNs may at times follow a more protracted clinical course<sup>16</sup>. Two reasons may explain this. One is that IPMN leads to the early diagnosis of invasive carcinoma, at a stage that is relatively more curable. And two, invasive tubular carcinomas arising from IPMNs may be biologically different despite the fact that they are morphologically indistinguishable from conventional ductal (tubular) carcinomas.

Clinically, IPMNs are also classified as “branch” vs “main” duct types. This classification is mostly based on the imaging findings of the tumors. It is, however, important to recognize the relevance of this classification, because in most institutions, branch-duct type IPMNs are managed conservatively (sometimes even “wait” and “watch” approach) as long as they are small (<3cm) and don’t show any mural nodules. These branch duct IPMNs often prove histologically to be adenomas with gastric/foveolar pattern and lack papilla formation. Although this classification is mostly for pre-operative evaluation of IPMNs, and is often no longer meaningful once the tumor is resected and evaluated pathologically, it is nevertheless important for pathologists to make a note of the extent of main duct involvement, which would serve as a feedback to the clinicians.

### **Intraductal oncocytic papillary neoplasms<sup>2</sup>**

Intraductal oncocytic papillary neoplasm is another group that can be considered under the heading of mass forming pre-invasive neoplasia of the pancreas. As are

IPMNs, intraductal oncocytic papillary neoplasms are intraductal tumors that lead to cystic dilatation of the ducts. Arborizing papilla formation is characteristic of intraductal oncocytic papillary neoplasms, although the complexity may vary from case to case or from area to area in a given case. In addition to the complexity of the papillae, intraepithelial lumen formation is also typical. Most characteristic finding, however, is the oncocytic nature of the cells.

Electron microscopy of intraductal oncocytic papillary neoplasms reveals the abundance of mitochondria. It has not been yet been determined whether these tumors should be regarded as a separate category or as a variant of IPMNs. Preliminary evidence suggests that their molecular characteristics are different than that of IPMNs. It is possible that, as in other organs such as the kidney where oncocytomas are biologically very different than histologically similar tumors, whatever is leading these cells to accumulate mitochondria may also give different biologic properties to these neoplasms.

### **Mucinous cystic neoplasms (MCNs)** <sup>17-20</sup>

The third category of mass forming preinvasive neoplasia is mucinous cystic neoplasms. Macroscopically, mucinous cystic neoplasms are characterized by a multilocular thick-walled cyst in the tail of the pancreas, adjacent to the spleen. In some cases, the cyst also contain papillary nodules. MCNs may sometimes get infected, develop purulent contents and may mimic pseudocysts. They are typically seen in perimenopausal females (mean age= 50 and >90% are females. The vast majority occurs in the tail of the pancreas. The cysts do not communicate with the ductal system and are therefore regarded as de-novo cysts. Presence of a distinctive ovarian-like stroma has become almost a requirement for the diagnosis of these tumors. It is pathognomonic for mucinous cystic neoplasms; present in most cases but not seen in other tumor types. Interestingly, it commonly expresses progesterone receptors. Rarely, even luteal-type cells may be seen in this ovarian-type stroma. We suspect that the ovarian stroma seen in MCNs may be a recapitulation of the periductal fetal mesenchyme which similarly condenses around the ducts of pancreas and liver in the developing fetuses <sup>21</sup>. As in IPMNs, there is a spectrum of cytoarchitectural atypia in MCNs, ranging from adenoma to CIS. Many times, an abrupt transition from one to the other may be seen, as in this example.

The grading and sub-classification of MCNs into adenoma, borderline and carcinoma have been an ongoing debate, which was resolved in the past few years. The groups from the AFIP, first in 1979 <sup>19</sup> and later in 1999 <sup>18</sup> have maintained that the grading of MCNs is not possible, and that these tumors are all low-grade malignancies, i.e mucinous cystadenocarcinoma, regardless of the degree of atypia or presence of invasion. In other words, in their experience, even the cases without any atypia could behave aggressively, and those with overt malignant features could follow an indolent course.

In 1999, however, groups from Johns Hopkins <sup>20</sup> and Europe (a multiinstitutional study) <sup>17</sup> contested this impression. They documented that grading accurately predicts

the clinical outcome, and that adenomas behave in a benign fashion in most instances. In our opinion, this discrepancy is related to sampling phenomenon. Carcinoma can be very focal in these tumors and may easily be missed unless the tumor is sampled extensively and examined thoroughly. This may explain why the AFIP experience, which is mostly based on consultation material, has failed to identify the relevance of grade. It is also our personal experience that the grade accurately predicts the outcome in most cases. Adenomas are invariably benign. However, we have seen MCNs with prominent papillary in-situ carcinomas that behaved in an aggressive fashion, despite the lack of any identifiable invasive carcinoma. Therefore, we ask for caution in cases with CIS.

**Summary of common findings in mass-forming pre-invasive neoplasia (IPMN, IOPN and MCN):**

IPMNs, IOPNs and MCNs share several characteristics. They are all *ductal* tumors. In the case of IPMNs and IOPNs it seems that the native ducts are involved by the process, whereas in MCNs, the process presumably forms de-novo cysts. In all, mucinous cells proliferate within these ductal units and secrete *mucin* to the lumen, which leads to *cystic* dilatation of these units, and in the case of IPMN (because the tumor is growing in the ductal system, and is usually located in the head of the organ) exudes from the ampulla of Vater. MCNs, on the other hand, may become infected, possibly because they do not communicate with the ducts and their contents are not drained. In all of these entities, proliferating mucinous cells may form *papillary* structures, and often the degree of cytologic atypia parallels the degree of proliferation. Presumably with accumulating genetic alterations, the proliferation acquires the capacity to *invade* and disseminate.

**Summary of differential diagnosis of mass-forming pre-invasive neoplasia (IPMN, IOPN and MCN):**

MCNs are seen almost exclusively in perimenopausal females (mean age, 50; >90% are females). They occur in the tail of the pancreas and do not communicate with the ductal system. Ovarian-type stroma is pathognomonic. IPMNs are seen predominantly in elderly patients and in the head of the pancreas. Mucin extrusion from ampulla of Vater is pathognomonic. They are intraductal tumors. IOPNs are characterized by their complex/arborizing papillae, intraepithelial luminae and oncocytic cells.

**Conclusion:**

Pre-invasive ductal neoplasia of the pancreas is an important category both clinically, in laboratory medicine as well as for cancer researchers. Our understanding of these tumors is still evolving. It is possible that these tumors will be instrumental in solving the puzzles of pancreatic carcinogenesis and bring us closer to the ultimate goal of preventing and curing these tumors.

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