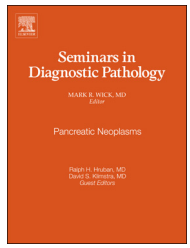
Seminars in Diagnostic Pathology 31 (2014) 452–466

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semdp



Intraductal neoplasms of the pancreas

Günter Klöppel, MD[a,*], *Olca Basturk, MD*[b], *Anna Melissa Schlitter, MD*[a], *Björn Konukiewitz, MD*[a], *Irene Esposito*[a]

[a]*Institute of Pathology, Technische Universität München, Munich, Germany*
[b]*Memorial Sloan-Kettering Cancer Center, New York, New York*

ARTICLE INFO

Keywords:
Pancreatic intraductal tumor
Intraductal papillary mucinous neoplasm
Intraductal tubulopapillary neoplasm
Prognosis
Genetics

ABSTRACT

There are three types of pancreatic neoplasms that predominantly have an intraductal growth pattern: the common, usually cystic, intraductal papillary mucinous neoplasms (IPMNs); the rare, usually solid intraductal tubulopapillary neoplasms (ITPNs); and the rare intraductal tubular pyloric gland-type adenoma. In addition to these three tumor types, pancreatic neoplasms with a usually solid growth pattern such as acinar cell carcinomas, neuroendocrine tumors, and undifferentiated carcinomas may present, though very rarely, as predominantly intraductally growing neoplasms. IPMNs can be subclassified into main duct and branch duct tumors; into low- and high-grade dysplasia groups; and into tumors with intestinal, pancreatobiliary, oncocytic, or gastric cellular differentiation. The intestinal-, pancreatobiliary-, and oncocytic-type IPMNs occur predominantly in the main duct of the head of the pancreas and more commonly progress to invasive adenocarcinomas. The gastric-type IPMNs are frequently multifocal, occur predominantly in the branch ducts of the uncinate process, and have a low risk of progressing to invasive carcinoma. The prognosis for patients with an IPMN depends largely on the subtype and the presence and the stage of an invasive carcinoma. ITPNs are nodular tumors, often in the pancreatic head, and composed of densely packed tubular glands. Molecular genetics reveal *KRAS*, *GNAS*, and *RNF43* as the most frequently mutated genes in IPMNs, while ITPNs show wild-type *KRAS*. Recent progress in genetic sequencing of pancreatic neoplasms and the identification of specific genetic mutations also holds promise for the future development of novel gene-based diagnostic tests in intraductal neoplasms of the pancreas that might even be used in preoperative conditions.

Neoplasms of the pancreas with intraductal growth

The category of pancreatic tumors that are designated intraductal neoplasms and arise in the main pancreatic duct or its branches includes the intraductal papillary mucinous neoplasms, the intraductal tubulopapillary neoplasms, and the intraductal tubular pyloric gland-type adenoma.[1] Apart from these main entities, there are usually solid tumors of the pancreas that, in rare cases, show predominantly intraductal growth. Reports have been published on predominantly intraductally growing acinar cell carcinomas,[2,3] neuroendocrine tumors,[4] and undifferentiated carcinomas.[5] Other than intraductal growth, the histologic, immunophenotypical, and

*Correspondence to: Institute of Pathology, Technische Universität München Ismaningerstr. 22, 81675 Munich, Germany.
E-mail address: guenter.kloeppel@lrz.tum.de (G. Klöppel).

http://dx.doi.org/10.1053/j.semdp.2014.08.005
0740-2570/

molecular characteristics of these typically solid neoplasms are identical to those of their conventional extra-ductal counterparts. In this review, we will mainly discuss the clinicopathological and genetic features of IPMNs and ITPNs.

Intraductal papillary mucinous neoplasms

Definition and classifications

Intraductal papillary mucinous neoplasm (IPMN)[1,6–9] is a category created to unify tumors that are grossly visible, mucin-producing, cystic tumors growing within the pancreatic ducts and forming papillary projections. These neoplasms had been previously reported in the literature under various terms such as intraductal papillary neoplasm,[10] ductectatic mucinous cystic neoplasm, mucinous duct ectasia,[11,12] mucin-producing tumor,[13,14] and adenoma(tosis) of the ducts.[15] IPMNs are currently classified based on their macroscopic appearance, grade of dysplasia, and cell type.

Classification by macroscopy

IPMNs are classified by imaging and macroscopic examination based on which pancreatic ducts are involved:

The *main duct-type IPMN* is characterized by a markedly dilated (often >1 cm), tortuous main pancreatic duct, that may be filled with mucin or solid but friable tissue (Fig. 1).[16] In 80% of the cases, main duct-type IPMNs affect the pancreatic head.

The *branch duct-type IPMN* manifests either as a cyst or a cluster of cysts without dilation of the main pancreatic duct (Fig. 2).[16] The cysts can be located anywhere in the pancreas but are more common in the head region, particularly in the uncinate process, and in the neck of the gland.[17–19] Computed tomography (CT) and magnetic resonance imaging (MRI) can be used to demonstrate communication between the cysts and the main pancreatic duct.

The mixed type of IPMN is a combination of the first two types.

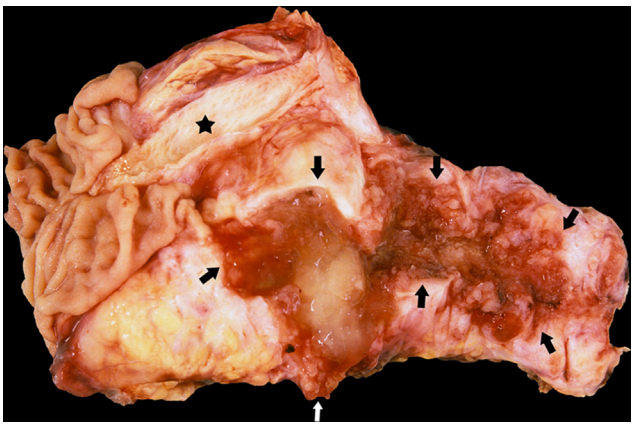


Fig. 1 – Main duct-type IPMN involving the entire pancreatic duct, filled with sticky mucin, with the adjacent normal common bile duct.

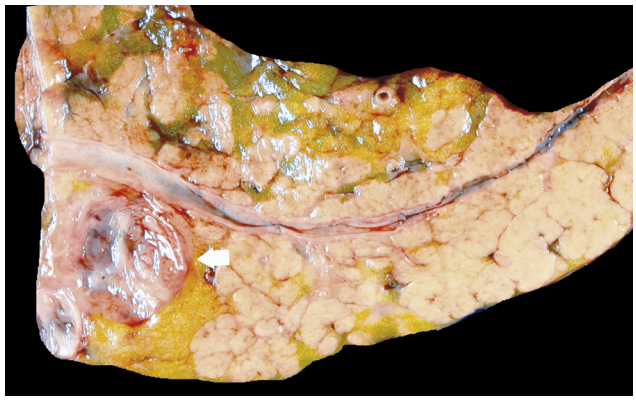


Fig. 2 – Branch duct-type IPMN characterized by a cluster of cysts within the parenchyma. Note the uninvolved main duct.

Classification by dysplasia

Based on the degree of cytoarchitectural atypia, the non-invasive components of IPMNs are subclassified as having low-, intermediate-, or high-grade dysplasia.[1,20]

Low-grade dysplasia is characterized by flat or papillary epithelium composed of tall columnar mucin-producing cells with basally located small nuclei. The cells display little or even no cytologic atypia, but may already show oncogenic alterations (see section Molecular genetics of IPMN and ITPN), and are thus regarded to have early neoplastic changes (Fig. 3).

Intermediate-grade dysplasia shows flat or papillary proliferations with focal or mild nuclear abnormalities, such as nuclear enlargement, nuclear crowding, hyperchromatism, and pseudostratification.

High-grade dysplasia is synonymous with carcinoma *in situ*, a term not advocated in the 2010 WHO classification, however.[1] High-grade dysplasia shows a predominantly (micro)papillary and cribriforming architecture, occasionally with luminal necrosis. Cytologically, these lesions have large cells; enlarged, irregular nuclei with prominent nucleoli; loss of polarity; and increased mitotic figures, including atypical forms. Tufting is a common characteristic feature (Fig. 4).

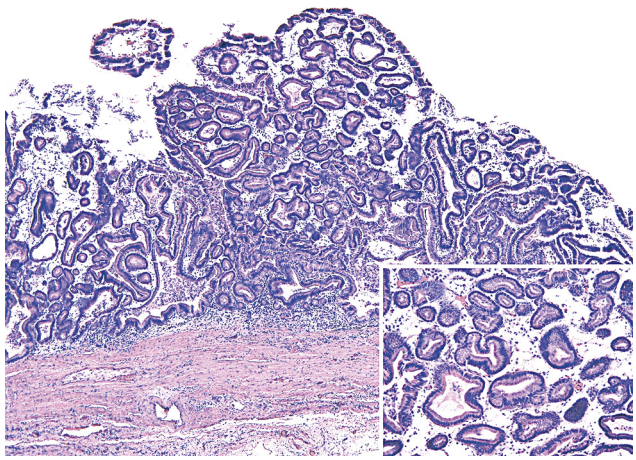


Fig. 3 – IPMN with low-grade dysplasia (gastric type).