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Clinicopathological features of pancreatic intraepithelial neoplasias and their relationship to intraductal papillary-mucinous tumors

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Abstract Pancreatic intraepithelial neoplasia (PanIN) is a recently proposed nomenclature for putative precursor lesions of pancreatic cancer, which are designated as PanIN-1 through -3 according to their increasing grade of dysplasia. A stepwise progression model of PanINs has been proposed, and multistep genetic alterations in PanINs are being investigated. PanIN-1A and PanIN-1B may remain unchanged for a long period. PanIN-3 potentially progresses toward invasive ductal carcinoma (IDC), and there are several case reports suggesting such progression. In these reported patients, PanIN-3 was found in specimens from partial pancreatectomies, and IDC manifested in the pancreatic remnant 17 months to 29 years after the surgery. We describe herein a patient with PanIN-3, in whom IDC manifested in the distal remnant pancreas 69 months after segmental pancreatectomy. Of the reported cases, including the present one, four of the patients were male and three were female, and the age at the first operation ranged from 46 to 70 years. Intraductal papillary-mucinous tumor (IPMT) is an entity that is distinct from PanIN. However, IPMTs of small size resemble PanINs morphologically. Loss of Dpc4 expression has been reported in the invasive component of IPMT, as well as in PanIN-3 and IDC. Analysis of mucin expression patterns has been reported, suggesting that, in practice, MUC1-positive MUC2-negative IPMTs may not be distinguishable from PanINs. There may be overlapping lesions between PanINs and IPMTs. Should the paradigm of the ductal origin of IDC be accepted, PanINs and a fraction of IPMTs would represent precursors of IDC.

Key words PanIN · IPMT · p53 · DPC4 · MUC

Introduction

Carcinogenesis of the exocrine pancreas has been intensively investigated, but many issues, including putative precursor lesions of pancreatic cancer, remain debatable.[1] Invasive ductal carcinoma (IDC), or ductal adenocarcinoma of the pancreas is the most common form of pancreatic cancer and has been assumed to originate from pancreatic duct epithelium.[2] Earlier pathohistological studies supported this assumption, and recent genetic analysis of the presumed precursor lesions by molecular technologies, as well as by immunohistochemistry techniques, revealed a multistep accumulation of genetic changes in these lesions. However, there has been confusion in the terminology used for proliferative epithelial lesions of the pancreas, and this situation has hampered interpretation of these studies using different terminologies. Today, in the era of genomics and proteomics, it has become indispensable to carry out studies under a standardized nomenclature. Pancreatic intraepithelial neoplasia (PanIN) is a recently proposed nomenclature for the putative precursor lesions of pancreatic cancer.[3] PanINs are divided into four categories: PanIN-1A, -1B, -2, and -3, according to the morphological features. It is assumed that normal epithelium develops into PanIN-1A, -1B, -2, and -3 sequentially and progresses toward IDC eventually. We review the literature on intraepithelial lesions of the pancreas both before and after the proposal of the nomenclature of PanIN and attempt to clarify the role of PanINs in carcinogenesis of the pancreas.

Because PanINs rarely develop clinical symptoms, the clinicopathological features of PanINs are scarcely documented. There are, however, reports of several patients with PanINs who underwent partial pancreatectomy and in whom IDC manifested in the pancreatic remnant months to years later.[4,5] As well as our literature review, we report herein a patient with PanIN-3 in whom IDC developed more than 5 years after segmental pancreatectomy. In this article, the clinicopathological features of PanINs with the subsequent development of IDC in the reported patients, including the present one, are reviewed.

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Table 1. New nomenclature for classification of duct lesions in the pancreas proposed at the Pancreas Cancer Think Tank (1999)[a]

Normal. The normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphophilic cytoplasm. Mucinous cytoplasm, nuclear crowding, and atypia are not seen.
Squamous (transitional) metaplasia. A process in which the normal cuboidal ductal epithelium is replaced by mature squamous or transitional epithelium without atypia.
PanIN-1A. Pancreatic intraepithelial neoplasia 1-A: these are flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin. The nuclei are small and round-to-oval in shape. When oval, the nuclei are oriented perpendicular to the basement membrane. It is recognized that there is considerable histologic overlap between nonneoplastic flat hyperplastic lesions and flat neoplastic lesions without atypia. TheTBore, some may choose to designate these lesions with the modifier ("PanIN/[L]-1A") to reflect the fact that the neoplastic nature of many cases of PanIn-1A has not been established.
PanIN-1B. Pancreatic intraepithelial neoplasia 1-B: these epithelial lesions have a papillary, micropapillary, or basally pseudostratified architecture, but are otherwise identical to PanIN-1A.
PanIN-2. Pancreatic intraepithelial neoplasia 2: architecturally, these mucinous epithelial lesions may be flat or papillary. Cytologically, by definition, these lesions must have some nuclear abnormalities. These abnormalities may include some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare, but when present are nonluminal (not apical) and not atypical. True cribriforming luminal necrosis and marked cytologic abnormalities are generally not seen, and when present should suggest the diagnosis of PanIN-3.
PanIN-3. Pancreatic intraepithelial neoplasia 3: architecturally, these lesions are usually papillary or micropapillary; however, they may rarely be flat. True cribriforming, budding off of small clusters of epithelial cells into the lumen, and luminal necroses should all suggest the diagnosis of PanIN-3. Cytologically, these lesions are characterized by a loss of nuclear polarity, dystrophic goblet cells (goblet cells with nuclei oriented towards the lumen and mucinous cytoplasm oriented toward the basement membrane), mitoses which may occasionally be abnormal, nuclear irregularities, and prominent (macro) nucleoli.

PanINs should be graded based on the highest-grade component of a lesion

[a] http://pathology.jhu.edu/pancreas_panin

Another tumor entity deriving from duct epithelium is intraductal papillary-mucinous tumor (IPMT) of the pancreas, characterized by the intraductal papillary growth of neoplastic cells producing mucin.[6,7] IPMTs are far less common than IDC; however, the incidence of IPMT has appeared to increase year by year, with awareness of IPMT being gained by physicians. IPMTs are categorized as adenoma, borderline tumor, and carcinoma, according to the grade of histological dysplasia,[6,7] and an adenoma-carcinoma sequence of IPMTs has been proposed.[8,9] IPMTs show slow progression in general, but some IPMTs can develop into invasive cancer. When IPMT becomes invasive, it shows either a tubular pattern, resembling IDC, or a muconodular pattern.[8] Whether or not IPMT can develop into IDC of the ordinary type remains unknown. Conversely, IPMTs of small size may lack recognizable mucin hypersecretion and duct dilatation, and therefore may resemble PanINs morphologically. However, the relationship of PanINs to IPMTs, especially to those without apparent mucin hypersecretion, has rarely been described. We attempted to determine the relationship of PanINs to IPMTs by a review of the literature.

Nomenclature

In 1999, a Pancreatic Cancer Think Tank, sponsored by the National Cancer Institute, was held at Park City, Utah, United States, and a new nomenclature for the classification of ductal lesions in the pancreas was agreed upon by the attending pathologists from North America and Europe. The term, "pancreatic intraepithelial neoplasia (PanIN)" was selected, and diagnostic criteria for each grade of PanIN were established. Briefly, PanINs are divided into three categories, PanIN-1 to PanIN-3, according to the degree of dysplasia (Table 1). PanIN-1 is further divided into PanIN-1A, with a flat morphological architecture, and PanIN-1B, with papillary architecture. PanIN-3 is the most atypical lesion, representing carcinoma in situ.[3]

Morphologic features of PanINs

According to the initially proposed definition, PanINs do not involve the main pancreatic duct, and they generally are too small to be seen grossly or by radiological imaging. In reality, however, PanINs originating from the secondary ducts may extend proximally and involve the main pancreatic duct and draw attention on imaging studies such as endoscopic retrograde cholangiopancreatography (ERCP).

Histological features of PanINs are well described in a Web page [http://pathology.jhu.edu/pancreas_panin]. This Web page contains examples of each grade of PanIN, as well as illustrations representing the classification system. The morphologic criteria for each sub-

type of PanIN are shown in Table 1. Typical microscopic features of various grades of PanIN are demonstrated in Fig. 1.

PanINs are most commonly found in the vicinity of invasive ductal carcinoma (IDC), but may be present in noncancerous pancreas. PanINs in the vicinity of IDC are supposedly distinguishable from intraductal extension of IDC and are presumed to be either transitional lesions of IDC or concurrent neoplastic lesions. An abrupt transition from a highly atypical lesion to normal duct indicates intraductal extension of IDC (Fig. 2). Other mimickers of PanINs are summarized in Table 2.

In the project to establish PanIN classification, the agreement on PanIN-2 classification among the pathologists was reportedly poor, implying that diagnostic criteria for PanIN-2 are not consistent.[3] Therefore, it is not feasible to characterize the category of PanIN-2 at this time. In this article, we focus mainly on PanIN-1 and PanIN-3 lesions for the purpose of clarity.

Earlier pathohistological studies of pancreatic epithelial lesions

The history of pancreatic epithelial lesions dates back to 1924, when Nakamura[10] described hyperplasia of duct epithelium of the pancreas. In 1954, Sommers et al.[11] examined 141 autopsy cases of pancreatic carcinomas and reported that, in 4 instances, there were transitions observed from a papillary pancreatic duct hyperplasia, situated most peripherally, to carcinoma in situ of ducts in an intermediate zone, around a central invasive adenocarcinoma of duct origin. It was also mentioned that hyperplasia of papillary or adenomatous type was found more frequently in pancreata with carcinomas as compared with nonneoplastic control cases. Since then, it has been hypothesized that some proliferative lesions of the ductal epithelium may progress toward IDC. Cubilla and Fitzgerald[12] examined pancreata in 227 patients with pancreatic cancer (100 pancreatectomy specimens and 127 autopsy specimens) and in 100 autopsies of patients with nonpancreatic cancer as controls. They reported that ductal papillary hyperplasia was three times more prevalent in pancreas cancer than in the controls. Marked atypia occurred in 20%, and carcinoma in situ occurred in 18% of the pancreas cancer patients, but neither change was seen in the control patients. They mentioned that marked atypia and carcinoma in situ appeared to be precursor lesions.[12] One of the most precise investigations of pancreatic ductal lesions was reported by Kozuka et al.[13] in 1979. They examined pancreatic specimens from 1174 autopsy patients, including patients with IDC, and found atypical hyperplasia in 29.2% of pancreata with infiltrating carcinoma and in 0.7% of pancreata without infiltrating carcinoma. The incidence of pancreatic cancer in their series was 2.0%, and atypical hyperplasia, papillary hyperplasia, and nonpapillary hyperplasia were found in 1.1%, 6.6%, and 18.1%, respectively.

Stepwise progression and molecular genetics of PanINs

A schematic diagram of the stepwise progression from normal duct to PanIN-1A, -1B, -2, and -3 is shown in Fig. 3.

When the earlier pathohistological studies of pancreatic epithelial lesions, as mentioned above, are interpreted according to the term "PanINs", as shown in Table 3, the incidence of PanIN-1A and PanIN-1B is estimated to be as high as approximately 20%, which is about ten times higher than that of IDC. These observations lead us to presume that PanIN-1A and PanIN-1B remain unchanged for a long period without further progression. The incidence of atypical lesions

Table 2. Mimickers of pancreatic intraepithelial neoplasia (PanIN)[a]

1. Cancerization of ducts. It was recognized that infiltrating carcinomas can extend into pancreatic ducts and ductules. When they do, they may mimic PanIN-3. An infiltrating carcinoma in close proximity to a duct lesion and an abrupt transition from a highly atypical lesion to normal duct epithelium should both suggest the possibility of cancerization of the duct or ductule. In these cases, serial (step) sections may be helpful in defining the relationship of the duct lesion to the infiltrating carcinoma.
2. Intraductal papillary mucinous neoplasms (IPMNs). IPMNs are mucinous epithelial neoplasms which involve the main pancreatic duct or its major branches. They are larger than PanINs and theTBore usually visible grossly or by radiologic imaging. IPMNs may extend into small ducts. In these cases serial (step) sections may be helpful in defining the relationship of the two lesions.
3. Mucinous cystic neoplasms. Mucinous cystic neoplasms are characterized by the presence of ovarian stroma and the absence of a connection to the duct system. These features and the larger size of mucinous cystic neoplasms help distinguish mucinous cystic neoplasms from PanINs.

Reactive changes. Reactive changes may mimic PanINs. The presence of significant inflammatory cell infiltrates, particularly when there are numerous polymorphonuclear leukocytes, should raise the possibility of reactive changes.

[a] http://pathology.jhu.edu/pancreas_panin

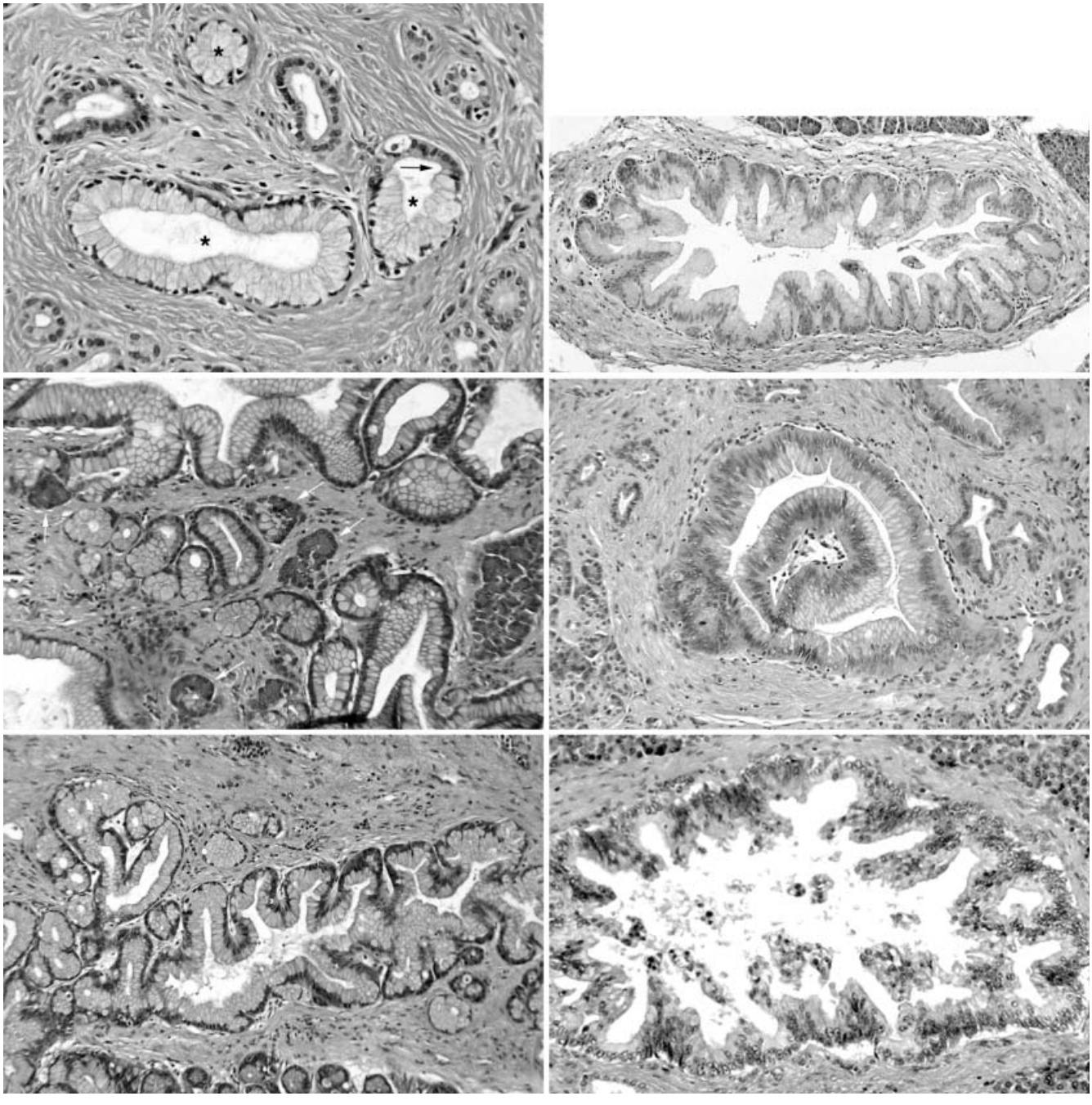

Fig. 1a–f. Microscopic features of pancreatic intraepithelial neoplasias (PanINs). PanINs are designated as PanIN-1 to -3 according to their increasing grade of dysplasia, and PanIN-1A and -1B are characterized by flat and papillary architectures, respectively. **a** PanIN-1A. Several small ducts (*asterisks*) show PanIN-1A. The *arrow* in the duct *on the right* indicates a junction between residual normal duct epithelium and the changes of PanIN-1. **b** PanIN-1A. Several peripheral ducts show PanIN-1A extending into a lobule of acinar tissue (*arrows*). **c** PanIN-1B. Several small intralobular ducts show PanIN-1B. **d** PanIN-2. There is pseudostratification of nuclei in the mucinous papillary epithelium. **e** PanIN-2. Both nuclear enlargement and pseudostratification are present in the mucinous papillary epithelium. **f** PanIN-3. The epithelium forms micropapillae with nuclei at the luminal surface; small groups of cells are shed into the lumen. H&E. Figure 1, courtesy of Dr. Daniel S. Longnecker, Lebanon, New Hampshire, USA

representing PanIN-3 may have been underestimated because tiny lesions of PanIN-3 are likely to be missed even by serial sectioning. The size of PanIN-3 when it initially invades the basement membrane and develops into IDC is not known, because this step can not be captured either in the clinical setting or in autopsy cases. We speculate that PanIN-3 is a transient step toward IDC, which, conceivably, lasts months to years, and that the speed of invasion accelerates markedly once a trigger of invasion is pulled.

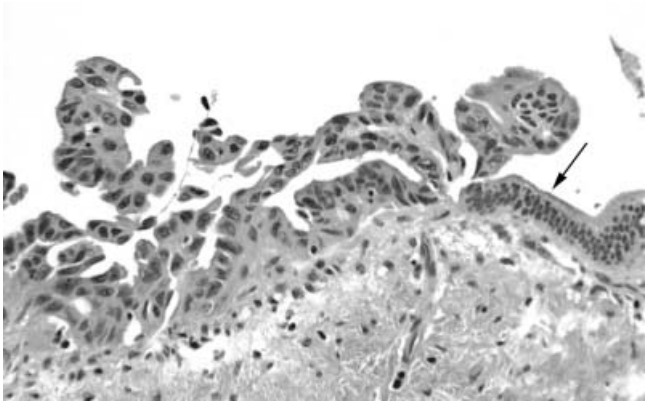

Fig. 2. Intraductal extension of invasive ductal carcinoma (IDC). The nearly normal ductal epithelium on the right (*arrow*) is abruptly replaced by highly dysplastic papillary epithelium. H&E. Figure 2, courtesy of Dr. Daniel S. Longnecker, New Hampshire, USA

The stepwise progression of PanINs was further supported by studies of molecular markers, including K-*ras*,[14–20] HER2/*neu*,[20–22] $p21^{WAF1/CIP1}$,[23] $p16^{INK4A}$,[18,24] p53,[20,25] and *DPC4*.[26,27] Point mutation of K-*ras* at codon 12 occurs early in the progression of PanINs, and the incidence of K-*ras* mutation increases progressively in accordance with the grade of PanINs.[14–20] Overexpression of HER2/*neu*, as well as $p21^{WAF1/CIP1}$, was also reported to occur early.[20–23] In almost all IDCs, inactivation of p16 occurs by loss of heterozygosity (LOH), homozygous deletion, or hypermethylation of the *p16* promoter region.[28] Loss of p16 expression was found in 30% of PanIN-1A, 27% of PanIN-1B, 55% of PanIN-2, and 71% of PanIN-3 lesions in a study by Wilentz et al.[24] Point mutation of *p16* at codon 110 occurs early, but was detected only in the lesions harboring the K-*ras* mutation.[18] Mutation of *p53* occurs as late as PanIN-2 to -3 stages.[19,20,25] *DPC4* (Deleted in Pancreatic Carcinoma, locus 4) is a tumor-suppressor gene located at chromosome 18q21.1,[29] and it is reportedly inactivated in over half of IDCs, either by homozygous deletion or by LOH.[30] Wilentz et al.[26,27] showed that 9 of 29 (31%) PanIN-3 lesions did not express Dpc4, while all of PanIN-1A, -1B, and -2 lesions that they evaluated expressed Dpc4.

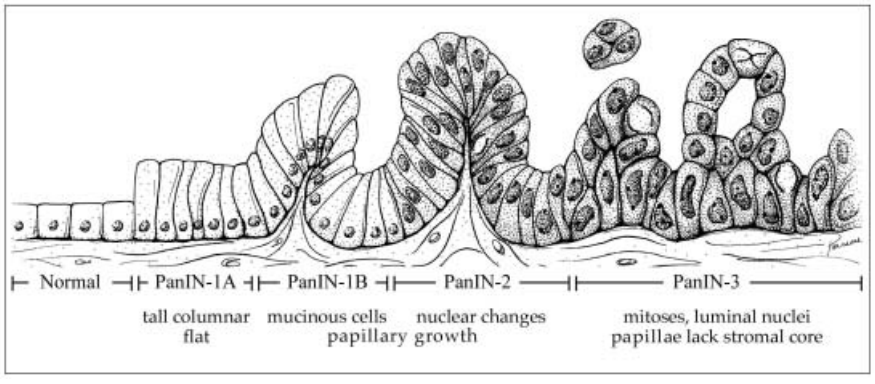

Fig. 3. Morphological diagram of pancreatic intraepithelial neoplasias (PanINs). A stepwise progression from normal duct epithelium to PanIN-1A, -1B, -2, and -3 is presumed. (Artwork by Jennifer Parsons, Baltimore, Massachusetts, USA. Reproduced with modification from reference 27 with permission from the publisher)

Table 3. A variety of older terms representing pancreatic intraepithelial neoplasia (PanIN)[a]

Squamous metaplasia. Epidermoid metaplasia, multilayered metaplasia
PanIN-1A. Pyloric gland metaplasia, goblet cell metaplasia, mucinous hypertrophy, flat duct lesion without atypia, mucinous ductal hyperplasia, simple hyperplasia, mucinous cell hyperplasia, flat ductal hyperplasia, nonpapillary epithelial hypertrophy
PanIN-1B. Papillary hyperplasia, papillary duct lesion without atypia, and ductal hyperplasia
PanIN-2. Atypical hyperplasia, papillary duct lesion with atypia, low-grade dysplasia, and some cases of moderate dysplasia
PanIN-3. Carcinoma in situ, intraductal carcinoma, high-grade dysplasia, severe dysplasia, and some cases of moderate dysplasia

Mucous metaplasia and pyloric gland metaplasia commonly involve small branch ducts or extend into lobules surrounding PanIN in ducts. Such involvement has been called adenomatoid or adenomatous hyperplasia, especially when the change dominates involvement of ductal epithelium. It is regarded as part of the spectrum of panIN-1

[a] http://pathology.jhu.edu/pancreas_panin

Table 4. Clinicopathological features of pancreatic intraepithelial neoplasias (PanINs) with subsequent manifestation of invasive ductal carcinoma

Case no.	Age (years)	Sex	Mode of operation	Histological diagnosis of resected specimen (Dpc4 status)	Type of SM (Dpc4 status)	Site of SM	Time to SM
1	70	F	PD	IDC with APH	IDC with liver metastasis	Body	9 Years
2	58	M	DP	Chronic pancreatitis with PanIN-3 (Dpc4−)	IDC (Dpc4−)	Head	10 Years
3	46	F	PD	Chronic pancreatitis with PanIN-3 (Dpc4+)	IDC (Dpc4+)	Tail	1 Year, 5 months
4	52	M	PD	Chronic pancreatitis with CIS	IDC	Body/tail	29 Years
5	68	M	PD	Chronic pancreatitis with CIS	IDC	Body/tail	9 Years
6	65	M	PD	IDC (Dpc4−) with PanIN-3 (Dpc4+)	IDC (Dpc4+)	Tail	3 Years
Present patient	68	F	SP	PanIN-3 (Dpc4−)	IDC	Body	5 Years, 9 months

Histological diagnosis is based on the terminology used in the original reports. Dpc4 status was available only for some patients
SM, subsequent manifestation; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; SP, segmental pancreatectomy; IDC, invasive ductal carcinoma; APH, atypical papillary hyperplasia; CIS, carcinoma in situ; Dpc4−, negative stain with anti-Dpc4 antibody; Dpc4+, positive stain with anti-Dpc4 antibody

Clinicopathological features of PanINs

There are few case reports of PanINs, and the clinicopathological features of PanINs are not known precisely. Therefore, we focused on pancreatic epithelial lesions with subsequent development of IDC, because the terminology of PanIN has been created under the concept that PanINs are precursors of IDC. In the literature, there are case reports of six patients suggesting the progression from PanINs to IDC (Table 4).[4,5,31] Four of these patients underwent proximal or distal pancreatectomy, and multifocal lesions representing PanIN-3 associated with chronic pancreatitis were found. IDC developed in the remnant pancreas 17 months to 29 years after the first pancreatectomy. The remaining two patients underwent pancreaticoduodenectomy for IDC. In one of the two patients, extensive atypical papillary hyperplasia, representing PanIN-3, involving the surgical margin was noted, and IDC developed in the remnant pancreas, with liver metastasis, 9 years after the surgery. According to recent analysis by Dpc4 immunohistochemical labeling in three of the reported patients, Dpc4 was expressed in both PanIN and subsequent IDC in one patient, was not expressed in either lesion in one patient, and was not expressed in the initial IDC but was expressed in the subsequent IDC in one patient. The third patient, with discordant expression of Dpc4, underwent pancreaticoduodenectomy, and multiple foci of PanIN-3 with intact Dpc4 expression were noted in the resected specimen, and IDC developed in the remnant pancreas 3 years later. The intact Dpc4 expression in the patient's second IDC suggested a second primary tumor, presumably deriving from the multifocal PanIN-3 lesions, rather than a recurrence of the first IDC, in which Dpc4 expression was lost.[31]

Recently, we experienced a patient with PanIN-3, in whom IDC manifested in the remnant pancreas 5 years and 9 months after segmental pancreatectomy. The case report is presented below.

Case report

The clinical course until the patient manifested IDC was reported previously.[32] Briefly, a 68-year-old woman, who had no history of cigarette smoking or alcohol abuse, received abdominal ultrasound at a mass screening in August 1995; a 1.4 × 0.7-cm hypoechoic lesion in the head of the pancreas was detected, and further examination was indicated. Her abdomen was normal upon physical investigation. Plasma amylase and lipase were normal. The tumor markers, carcinoembryonic antigen (CEA), DU-PAN-2, and carbohydrate antigen (CA) 19-9, were within normal ranges. Endoscopic retrograde pancreatography showed segmental narrowing, 5 mm in length, of the main pancreatic duct between the

head and body of the pancreas. Imaging studies with computed tomography (CT) and magnetic resonance imaging (MRI) confirmed the pancreatic mass first detected by abdominal ultrasound. Angiography revealed no abnormal findings.

With a diagnosis of pancreatic mass possibly related to pancreatic carcinoma, an exploratory laparotomy was carried out, on October 26, 1995. An elastic soft mass, approximately 1 cm in size, was palpated in the neck of the pancreas. The rest of the pancreas was of soft consistency and of normal appearance. A segmental pancreatectomy was performed and the mass was excised. Intraoperative histological examination showed localized fibrosis of the pancreas, and further evaluation awaited investigation with permanent sections, which revealed papillary lesions in a segment of the main pancreatic duct. Localized fibrosis was observed in a lobule of the exocrine gland draining into the tributary that was obstructed by the epithelial lesion. A high-power view showed stratified pleomorphic cells with severe atypia, representing PanIN-3 (Fig. 4a). Multiple sections of the specimen showed no evidence of invasion, but revealed papillary proliferation without remarkable dysplasia at the distal resection margin (not shown). By immunohistochemical staining with monoclonal mouse antibody against human p53 protein (DO-7; Dako, Glostrup, Denmark) and rabbit affinity-isolated antibody against human Ki-67 peptide (Ki-67 antigen; Dako), the PanIN-3 lesion showed positive nuclear staining for p53 protein (Fig. 4b), as well as for Ki-67 antigen (not shown) exclusively in the neoplastic cells. The specimen was recently immunolabeled with mouse monoclonal antibody against amino acids representing full-length Smad4 (Dpc4) of human origin (B-8; Santa Cruz Biotechnology, Santa Cruz, CA, USA), and with a rabbit polyclonal antibody against the human c-erbB-2 (HER2/*neu*) product (A0485; Dako). Focal loss of Dpc4 expression was found in the epithelial lesion with severe dysplasia representing PanIN-3, while the surrounding papillary lesion with lower-grade dysplasia showed intact Dpc4 expression (Fig. 4c). No overexpression of HER2/*neu* was noted in the PanIN-3 lesion (not shown).

The patient was discharged home after a satisfactory recovery. She remained in good physical condition for over 5 years; however, she has suffered from left upper abdominal pain since July 2001. The values for CEA and CA19-9 were 5.3 ng/ml and 106.3 U/ml, respectively, on October 18, 2001, and were further elevated, to 33.7 ng/ml and 113.2 U/ml, respectively, on January 7, 2002. CT, on November 6, 2002, showed a low-density mass in the distal remnant of the pancreas invading the colon, stomach, and mesentery of the small intestine (Fig. 5). Encasement of the splenic artery and common hepatic artery were also noted. Swelling of

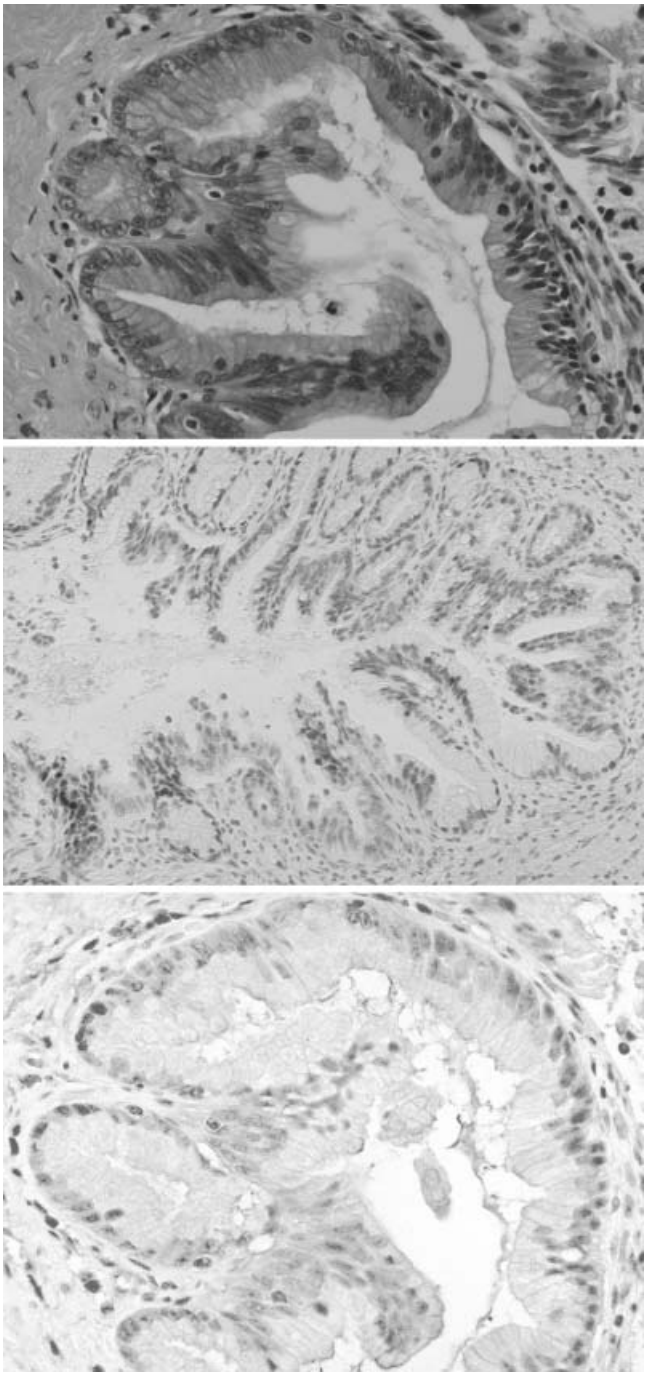

Fig. 4a–c. Papillary proliferative lesion in the main pancreatic duct in the present patient. **a** Stratified pleomorphic cells with severe dysplasia represent PanIN-3. **b** Overexpression of *p53* was found in the epithelial lesion with severe dysplasia by immunolabeling for anti-p53 antibody. **c** The epithelial lesion with severe dysplasia did not express Dpc4, while the surrounding papillary lesion with lower-grade dysplasia showed intact Dpc4 expression by immunolabeling for anti-Dpc4 antibody. **a** H&E, ×100; **b** ×40; **c** ×100

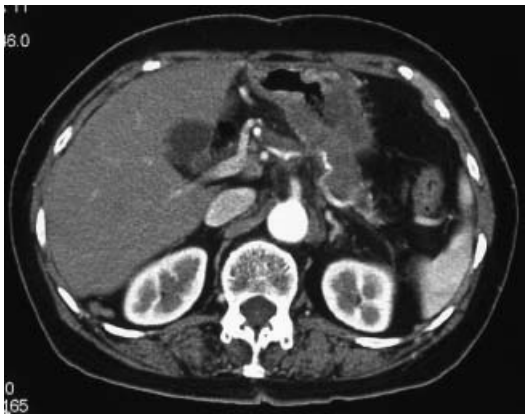

Fig. 5. Abdominal computed tomography (CT) scan on November 6, 2002, in the present patient. A low-density mass in the distal remnant of the pancreas is noted. Encasement of the splenic artery is marked

regional lymph nodes on CT suggested metastatic lymphadenopathy. A diagnosis of IDC of the remnant pancreas with extensive invasion into adjacent structures was made, and the patient is receiving chemotherapy at present.

The clinicopathological features of the reported patients with PanINs with subsequent manifestation of IDC are summarized in Table 4. There were four male and three female patients. The age at the time of the first pancreatectomy ranged from 46 to 70 years (mean, 61 $\pm$ 7.7 years). When subsequent development of IDC was identified in the five patients who did not have IDC initially, the ages of these patients ranged from 47 (or 48) to 81 years, with a mean age of approximately 69 years, which is comparable to the age at incidence of primary IDC, with a peak in the seventh decade of life. Proximal pancreatectomy by means of the Whipple procedure was performed in five patients, distal pancreatectomy in one, and segmental pancreatectomy in the present patient. While PanIN lesions were initially found in the head of the pancreas in the majority of the patients, sites of subsequent development of IDC were predominantly the distal portion of the pancreas, reflecting the mode of the first operation. The history of cigarette smoking in these patients was not defined. Alcohol abuse was documented in one of the reported patients. One patient underwent surgery for idiopathic recurrent pancreatitis and another for chronic relapsing pancreatitis. PanIN-3 is not likely to develop specific clinical symptoms to draw the attention of physicians. However, PanINs associated with pancreatitis may cause abdominal discomfort or pain. Whether or not the condition of pancreatitis with diffuse fibrosis is related to PanIN is not known. In the patient we reported here, PanIN-3 was associated with localized fibrosis due to obstruction of a secondary duct by the PanIN lesion.

Diagnosis and treatments of PanINs

Conventional imaging studies, including ERCP, may provide a clue to the diagnosis of PanINs, when particular interest in PanINs is taken. Cytological examination of pancreatic juice may contribute not only to the detection of occult lesions in the pancreatic duct system but also to the evaluation of the degree of cytonuclear atypia.[33] Assessments of telomerase activity and *p53* mutation, as well as K-*ras* mutation, in pancreatic juice samples are also reported.[34–37] It is hoped that peroral pancreatoscopy will open a new epoch in the diagnosis of pancreatic tumors of ductal origin, especially of IPMTs.[38] However, PanINs in peripheral ducts may not be visible by this technique. Intraductal ultrasound (IDUS) through pancreatic ducts is another novel modality,[39] which may be capable of detecting PanINs.

Pancreatic resection should be indicated when the results of careful and meticulous examinations point to the diagnosis of PanIN-3, which is a potential precursor of IDC. Nevertheless, we have to admit that it is difficult to make a definitive diagnosis of PanIN-3 by conventional methods other than surgical excision. New modalities, including genetic and cytological analysis of pancreatic juice, as well as pancreatoscopy and IDUS, are expected to lead to the detection and accurate diagnosis of PanINs.

When PanINs are observed at the surgical margin, interpretation of these lesions requires particular caution, because PanINs of low grade in the vicinity of PanIN-3 and IDC may be genetically advanced lesions.[18] The papillary lesion at the surgical margin in the patient we presented here was not associated with remarkable dysplasia, but may have been the origin from which IDC developed in the distal remnant of the pancreas.

Multifocal lesions of PanIN-3 in the resected specimen of the pancreas imply the existence of similar lesions in the pancreatic remnant. When such lesions are identified in a specimen from a partial pancreatectomy performed for chronic pancreatitis or for other reasons, these patients should be considered at risk of IDC developing in the pancreatic remnant, and careful periodic follow-up studies of the remnant pancreas are recommended for at least 10 years.

Relationship of PanINs to IPMTs

IPMT is considered to be an entity that is distinct from IDC and from PanINs.[6,7] It is well known that Ohhashi et al.[40] reported four cases of "mucin-producing cancer of the pancreas" in 1982, and that subsequent reports of this type of pancreatic tumor have led to the recognition of IPMT. Since the study of Ohhashi et al.,[40] the term

"carcinoma in situ" has been frequently used for IPMTs with severe atypia similar to carcinoma at the cytonuclear level, but without invasion.[8] There are several reports of carcinoma in situ of the pancreas, and some of these reported cases are considered IPMTs.[41,42]

IPMTs often arise from main pancreatic ducts or secondary ducts, while PanINs originate from the smaller ducts or ductules, according to the original definition. Judging from the definition, one of the differences between IPMTs and PanINs is the size of the ducts that they arise from. It might be hypothesized that IPMTs originating from proximal portions of the pancreatic duct system tend to spread intraductally, because the fibrous walls of the ducts are thick and firm in the main and major branch ducts, while PanINs tend to initiate invasion without a grossly visible intraductal component because the ductal walls are so thin in the intralobular ducts and ductules that they can be easily penetrated. This hypothesis is very attractive, but is not compatible with reports describing that IPMTs involving the main pancreatic duct show more aggressive pathologic features[43] and have stromal invasion more frequently[9] than IPMTs of the secondary ducts or branch ducts. There appear to be factors other than the thickness of the duct wall that affect invasion of the tumor.

IPMTs are generally characterized by mucin hypersecretion, and can be differentiated from PanINs. However, intraductal papillary tumor, which is an older term for IPMT without mucin hypersecretion,[2,7] is encompassed by the term "IPMT", and the differential diagnosis of PanINs from this type of IPMT is problematic. For example, if a tiny papillary lesion, initially representing PanIN-1B, had spread along a small-caliber duct toward the proximal duct and eventually obstructed the proximal duct, causing duct dilatation, it would be diagnosed as IPMT. Thus, when an IPMT is of small size and lacks recognizable mucin secretion, it is impossible to differentiate these two entities morphologically.

Mutation of K-*ras* at codon 12 was reportedly observed in 31% to 100% of IPMTs.[44–49] Frequent HER2/*neu* overexpression has been reported in IPMTs as well as in PanINs.[20–22,46] Sessa et al.[46] reported that overexpression of p53 and point mutation of *p53* was found in 8 (31%) and 2 (8%) of 26 patients with IPMTs, respectively. In contrast, overexpression of p53 was not found in 18 patients with IPMTs, but was found in 1 patient with an invasive variant of IPMT by Kawahira et al.,[50] and *p53* mutation was detected in none of 26 patients with IPMTs in the series of Hoshi et al.[47] Point mutation of *p16* was not detected in any of 10 patients with IPMTs in the series of Moore et al.[51] Interestingly, loss of Dpc4 expression was found in an invasive component of tubular type deriving from IPMT, while Dpc4 protein was consistently expressed in IPMT, except for the invasive component.[52] Loss of Dpc4 expression may be involved in the mechanism of invasion by a certain population of IPMTs, as well as being involved in the mechanism of progression from PanIN-3 to IDC.

Subtypes of mucin expression in IPMTs have been studied by immunohistochemistry,[53–56] and the MUC1-negative MUC2-positive type was reported to be most common by Osako et al.,[54] Yonezawa et al.,[55] and Lüttges et al.[56] It was also demonstrated, by in situ hybridization, that MUC2 immunoreactivity paralleled MUC2 mRNA expression.[57] In contrast, in a study by Terada et al.,[53] eight of nine IPMTs were of MUC1-positive MUC2-negative type. The reason for these discordant results is unclear. IDC is reported to be MUC1-positive and mostly MUC2-negative.[53,56] Lüttges et al. reported that none of the 32 lesions of PanIN-1 and none of the 18 lesions of PanIN-2 in the vicinity of IDCs were stained with MUC1, while all of the IDCs they evaluated were stained with MUC1.[56] In IPMTs, MUC1 positivity was observed exclusively in carcinomas, while none of the adenomas or borderline tumors exhibited MUC1 expression.[56] The expression of MUC1 may be related to the mechanism of carcinogenesis in PanINs, as well as in IPMTs, and MUC1 expression in PanIN-3 remains to be determined. It has been suggested that MUC2-positive IPMTs are distinguishable from PanINs and are compatible with precursors of mucinous noncystic carcinoma.[56] IPMT of oncocytic type may represent an individual entity according to a study showing the focal expression of both MUC1 and MUC2 in these tumors.[56]

Yamaguchi et al.[58] reported "in situ carcinoma" lesions that were associated with mucinous cystadenoma in two male patients. The mucinous cystadenomas in their report lacked "ovarian-like stroma" and would be interpreted as IPMTs according to the current hitological criteria. The microscopic features of "in situ carcinoma" lesions in their report were similar to those of PanIN-3. In one of the two patients, who underwent distal pancreatectomy at the age of 55 years, IDC developed 7 years later in the pancreatic remnant.[59] Subsequent manifestation of IDC suggests progression from concurrent PanIN lesions or from multifocal lesions of IPMT. It is possible that PanINs and IPMTs coexist in the same pancreas, and whether or not PanINs develop more frequently in pancreata harboring IPMTs than in normal pancreata is another issue to be investigated.

Perspectives

Although the number of reported cases of PanINs with subsequent development of IDC is limited, the clinico-

pathological features of these lesions are not different from those of ordinary cases of IDC. Accumulation of case reports of PanIN will further clarify the true nature of PanINs.

Based on studies of mucin expression patterns in pancreatic tumors of ductal phenotype, IPMTs of the MUC2-positive type correspond to an entity that is distinct from PanIN and can be differentiated from PanINs by mucin analysis. Theoretically, however, MUC1-positive MUC2-negative IPMTs of small size, which may be as rare as PanIN-3 without IDC, and hard to detect, cannot be differentiated from PanINs, and it is possible that there are overlapping lesions between PanINs and IPMTs. Further investigation of mucin expression patterns in PanIN lesions may provide a clue to clarify the relationship of PanINs to IPMTs.

It has long been believed that IDC originates from the epithelium of peripheral ducts or ductules. If this were always the case, PanINs as precursors of IDC could be differentiated from most IPMTs by the site where the lesions originated. However, there is no strong evidence to deny that some IDCs originate from the epithelium of proximal pancreatic ducts. Another conceivable measure to differentiate PanINs from IPMTs morphologically is discrimination by the size of the lesion. For example, a diagnosis of PanIN is to be given if the lesion is smaller than a certain size, i.e., 5 mm, while a diagnosis of IPMT is to be given if the lesion is larger than another certain size, i.e., 10 mm, and lesions between these sizes are to be considered overlapping lesions. Further study is needed to verify these hypothesized criteria for the differential diagnosis of PanINs from IPMTs.

In conclusion, should the paradigm of the ductal origin of IDC be accepted, PanINs and a fraction of IPMTs would represent precursors of IDC.

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