Pancreatic Intraepithelial Neoplasia

8

The pancreatic intraepithelial neoplasia (PanIN) nomenclature and classification system, used to describe the microscopic epithelial precursor lesions of pancreatic ductal adenocarcinoma, was first proposed in 1994 [1], modified in 1999 [2], and further refined in 2004 [3]. This PanIN nomenclature replaced at least 70 different diagnostic terms for the same entities [3]. Such previous descriptive terms included mucinous hyperplasia, mucinous cell hypertrophy, papillary hyperplasia, mucinous metaplasia, atypical hyperplasia, and dysplasia.

It is now well recognized that the morphological progression of PanIN to invasive ductal adenocarcinoma mirrors the molecular progression, which is often referred to as the 'PanINgram' [4]. The average time taken for genetic progression from an initiating mutation in a normal ductal epithelial cell, through PanIN, to invasive ductal adenocarcinoma has been estimated to be 11.7 years (see Chap. 9, Sect. 9.13) [5]. However, most low-grade PanINs never progress to invasive carcinoma. A recent study has suggested that PanIN may seed along the ductal system [6].

PanIN is one of the three main precursors of pancreatic invasive adenocarcinoma. The two other precursors are mucinous cystic neoplasm (see Chap. 16) and intraductal papillary neoplasm (see Chap. 17). These are both macroscopic lesions, in contrast to the microscopic nature of PanIN.

PanINs may arise in any part of the pancreatic duct system, including the main pancreatic duct, and until recently were classified into PanIN-1A, PanIN-1B, PanIN-2, and PanIN-3, according to the degree of architectural and cytological atypia [2]. The normal ductal lining of nonmucinous, cuboidal to low-columnar epithelial cells (see Chap. 1, Sect. 1.4.3) is replaced initially by tall columnar mucinous epithelium showing minimal cytological atypia (PanIN-1A). In PanIN-1B, this minimally atypical tall columnar mucinous epithelium is thrown into micropapillae or papillae. PanIN-2 is characterized by increasing cytological atypia, and in PanIN-3 there is a more complex architecture and severe cytological atypia. More than one type of PanIN may be seen in a single duct. Although PanIN-1 may show an abrupt transition with normal ductal epithelium (Fig. 8.1), this does not occur with high-grade PanIN.

Following a consensus meeting in Baltimore, it was recommended that this three-tiered grading system should be replaced by a two-tiered system [7], with PanIN-1 and PanIN-2 being categorized as low-grade PanIN, and PanIN-3 as high-grade PanIN. This two-tiered system has now been included in the 2019 WHO classification of tumors of the pancreas, where it is also referred to as 'glandular intraepithelial neoplasia, low grade' and 'glandular intraepithelial neoplasia, high grade' [8].

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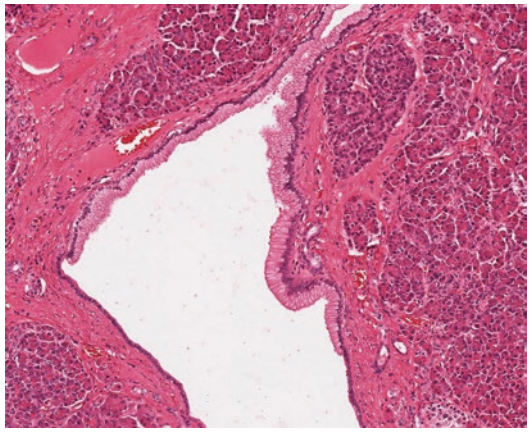

Fig. 8.1 Low-grade PanIN (formerly PanIN-1A): there is abrupt transition between the normal duct epithelium (*bottom*) and this flat lesion lined by tall columnar cells with supranuclear mucin and small round basal nuclei

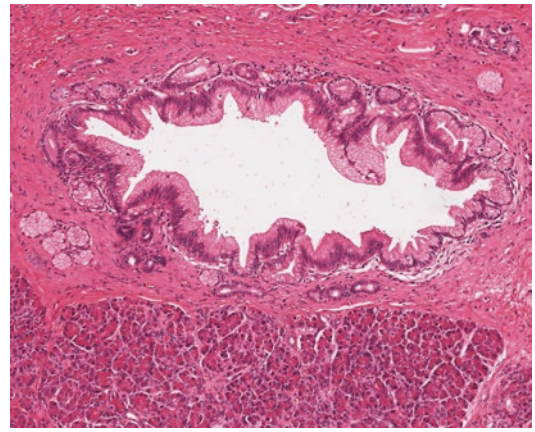

Fig. 8.2 Low-grade PanIN (formerly PanIN-1B): this papillary/micropapillary lesion is lined by tall columnar cells identical to those seen in Fig. 8.1

8.1 WHO Classification

Pancreatic (glandular) intraepithelial neoplasia (low grade and high grade) is included in 'benign epithelial tumors and precursors' in the 2019 WHO classification of tumors of the pancreas [8].

8.2 Classification and Microscopy

8.2.1 Low-grade PanIN (Figs. 8.1–8.3)

These are epithelial lesions composed of tall columnar cells with varying amounts of supranuclear mucin and mild-to-moderate cytological atypia. The epithelium may be flat or have a papillary or micropapillary architecture. The nuclei may be small, uniform, round to oval, and basally located (formerly PanIN-1) or show some nuclear abnormalities, including loss of nuclear polarity, nuclear crowding and pseudostratification, nuclear enlargement, hyperchromatic nuclei, and small nucleoli (formerly PanIN-2). Mitotic figures are rare, but when present are basal and not atypical.

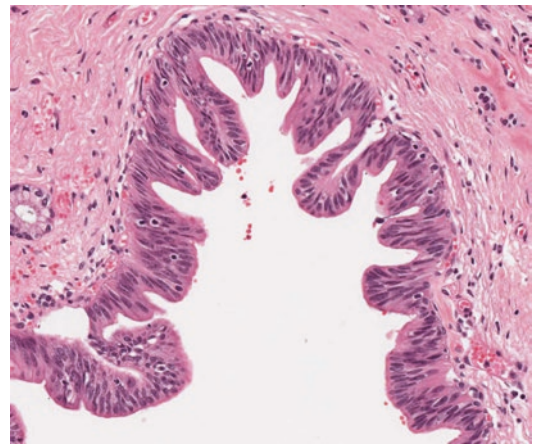

Fig. 8.3 Low-grade PanIN (formerly PanIN-2): this micropapillary lesion is lined by columnar cells that lack intracytoplasmic mucin and show nuclear crowding and pseudostratification with mild-to-moderate nuclear atypia

8.2.2 High-grade PanIN (Fig. 8.4)

This is also known as carcinoma in situ. These epithelial lesions are usually papillary and/or micropapillary, but rarely may be flat. They may show a cribriform architecture, there may be luminal necrosis, and small clusters of epithelial cells may bud off into the lumen. There is significant cytological atypia with loss of nuclear

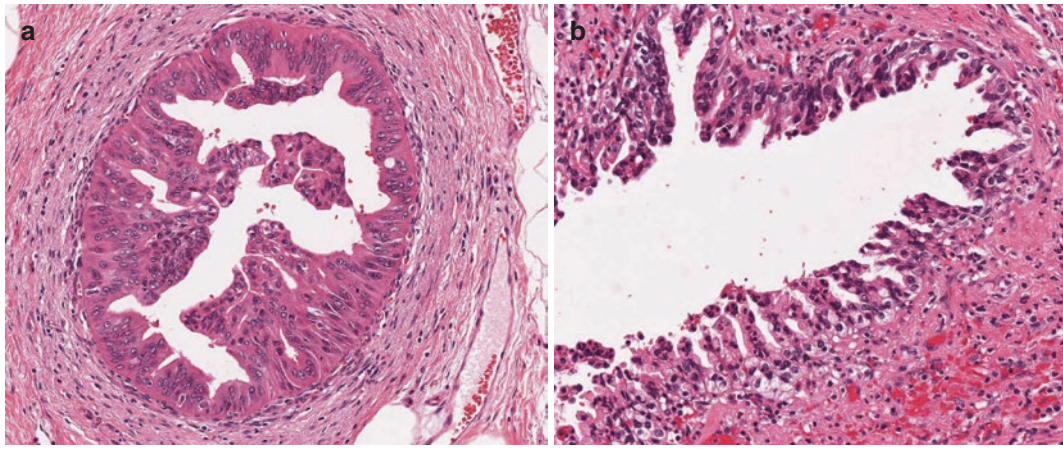

Fig. 8.4 High-grade PanIN (formerly PanIN-3): there is a complex papillary, almost cribriform, architecture with loss of nuclear polarity and marked nuclear pleomorphism with prominent nucleoli (**a**). Single cells and occasional clusters of cells can be seen budding off the numerous micropapillae in this lesion (**b**)

polarity, marked nuclear pleomorphism, and prominent nucleoli. Mitotic figures can be present and may occasionally be abnormal.

8.3 Variants of PanIN

Three variants of PanIN have been described, *intestinal PanIN*, *oncocytic PanIN* [9] and *foamy variant of PanIN* [10]. However, all were described in pancreata with associated invasive adenocarcinoma of the same phenotype, namely intestinal-type adenocarcinoma, oncocytic carcinoma, and foamy gland pattern of adenocarcinoma, respectively (see Chap. 9, Sects. 9.6.2 and 9.8). Therefore, it is possible that some cases may represent cancerization of ducts (see Sect. 8.6.2) and/or (for the intestinal and oncocytic variants) residual intraductal papillary neoplasia (see Sect. 8.6.1 and Chap. 17), rather than PanIN.

In intestinal PanIN, the duct lining shows an intestinal phenotype with pseudostratified tall columnar cells, scattered goblet cells, and elongated cigar-shaped nuclei. In oncocytic PanIN, the small ducts are lined by cuboidal or columnar cells with pale or eosinophilic granular cytoplasm and large vesicular nuclei with prominent nucleoli. The foamy variant of PanIN (Fig. 8.5) differs from conventional PanIN in that involved small ducts may be markedly dilated and the lining cells have abundant foamy cytoplasm, often with small irregular hyperchromatic nuclei. Foamy cells alternate with non-foamy cuboidal or columnar cells in the same duct. On mucin histochemistry (alcian blue, PAS-diastase, or mucicarmine), the foamy cells show band-like staining

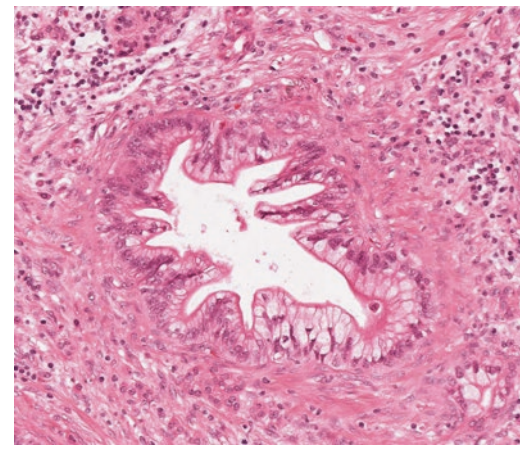

Fig. 8.5 Foamy variant of PanIN: the columnar cells have abundant foamy cytoplasm with luminal cytoplasmic condensation

in the apical cytoplasm, while the rest of the cytoplasm only shows focal staining.

8.4 Associations

Low-grade PanIN may occur in normal pancreas (including heterotopic pancreas) and diseased pancreata. The frequency appears to correlate with age: low-grade PanIN is rare in patients younger than 40 years but increases in frequency after 40 years of age. Low-grade PanIN may be seen in chronic pancreatitis and in the background of pancreata with ductal adenocarcinoma or ampullary neoplasia, as well as less common neoplasms such as mucinous cystic neoplasm, serous cystic neoplasm, solid pseudopapillary neoplasm, pancreatic endocrine neoplasm, and acinar cell carcinoma.

In contrast, high-grade PanIN is very rare in the normal pancreas but may occasionally be seen in (nonhereditary) chronic pancreatitis and in fatty replacement of the pancreas [11]. High-grade PanIN is most commonly described in the background of pancreata with invasive ductal adenocarcinoma. However, this may represent intraductal extension of the invasive carcinoma along the duct (so called cancerization of ducts—see Sect. 8.6.2) and not high-grade PanIN [12]. One study has shown that such duct cancerization can extend for more than 2cm along the ducts [13].

8.4.1 Hereditary Pancreatitis and Familial Pancreatic Cancer

PanINs are frequently found in patients with hereditary pancreatitis (see Chap. 6, Sect. 6.3) and includes both grades of PanIN. They occur at a younger age (median age of 24 years), and their frequency is much higher than in the pancreata of normal subjects at the same age or in patients with alcoholic chronic pancreatitis [14].

PanINs are also more common in patients with familial pancreatic cancer (see Chap. 6, Sect. 6.5) than in patients with sporadic pancreatic cancer [15].

8.5 Lobulocentric Atrophy

Pancreatic parenchyma adjacent to PanINs often shows varying degrees of atrophy and/or fibrosis referred to as lobulocentric atrophy [16]. Lobulocentric atrophy (Fig. 8.6) is characterized by loss of acinar parenchyma in the lobule surrounding the PanIN, acinar to ductal metaplasia, fibrosis, and aggregates of islets (see Chap. 5, Sect. 5.5). It occurs with both grades of PanINs and is seen particularly in elderly patients and in those with a strong family history of pancreatic cancer (see Chap. 6, Sects. 6.4 and 6.5).

8.6 Differential Diagnosis

8.6.1 Intraductal Papillary Mucinous Neoplasm

PanIN lesions are too small to be seen grossly or by imaging techniques. In contrast, intraductal papillary mucinous neoplasms (IPMNs) can be detected clinically and radiologically (see Chap. 17). IPMNs involve the main pancreatic duct and branch ducts, and produce copious amounts of mucin, which may be seen oozing from the ampulla of Vater. In addition, the papillae of IPMN can be grossly visible and are taller and more complex than the papillae of PanIN (Table 8.1).

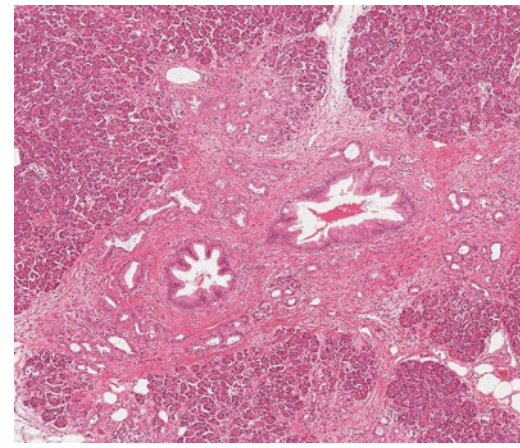

Fig. 8.6 Lobulocentric atrophy associated with low-grade PanIN: there is acinar to ductal metaplasia and fibrosis in the lobule around the PanIN

Table 8.1 Potential criteria for distinguishing pancreatic intraepithelial neoplasia (PanIN) from intraductal papillary mucinous neoplasia (IPMN)

	PanIN	IPMN
Clinically detected	No	Yes
Grossly visible	No	Yes
Mucus oozes from ampulla of Vater	No	Yes
Duct size	Usually <5 mm diameter	Usually >5 mm diameter
Intraluminal mucin	Minimal	Abundant
Growth pattern	Flat or papillae	Predominantly papillary, rarely flat
Papillae	Microscopic	Taller, more complex, and grossly visible
Associated invasive adenocarcinoma	Conventional type	Conventional type or colloid carcinoma

PanIN lesions are defined as involving ducts less than 5 mm in diameter, whereas IPMNs involve the main pancreatic duct or branch ducts and usually produce a lesion greater than 5 mm in diameter. The epithelium in PanIN almost always shows gastric foveolar differentiation. In contrast, the epithelium in IPMN can show gastric, intestinal, or pancreatobiliary differentiation, and the epithelium in intraductal oncocytic papillary neoplasm (IOPN) shows oncocytic differentiation. Therefore, lesions with intestinal or oncocytic differentiation are most likely to be IPMN or IOPN, respectively.

It is worth noting that low-grade PanIN may be found in retention cysts (see Fig. 19.10b and Chap. 19, Sect. 19.3.1), which can mimic gastric-type IPMN, whereas, conversely, IPMNs may extend into the adjacent smaller ducts and mimic PanIN (see Fig. 17.10 and Chap. 17). In retention cysts, there is usually normal ductal epithelium as well as the PanIN in the same cyst, but IPMN can give rise to similar appearances. Moreover, the cause for obstruction and formation of retention cysts is not always apparent. Step-sections can be used to determine whether or not a lesion in a small duct is in continuity with, and shares the same lining epithelium as, a larger lesion that fulfills the criteria for IPMN.

The distinction between a large, low-grade PanIN and a small gastric-type IPMN may not always be possible, both of which can involve branch ducts, share similar morphological features, and have similar mucin profiles. It may be helpful to use the term 'intraductal/intraepithelial neoplasm of low grade, either PanIN or IPMN' in such circumstances (see Chap. 23, Sect. 23.3.2) [17]. However, the distinction between PanIN and gastric-type IPMN appears not to be prognostically significant if the lesion is low grade and has been completely excised.

8.6.2 Cancerization of Ducts

Invasive pancreatic ductal adenocarcinoma and, on occasion, metastatic adenocarcinoma can invade and grow along the lumina of nonneoplastic ducts (see Chap. 9, Sect. 9.10), so called 'cancerization' of ducts [12, 13], and may mimic high-grade PanIN (Fig. 8.7). There is usually a sharp transition between the normal duct epithelium and the cancer, whereas high-grade PanIN usually either involves the whole duct or merges with low-grade PanIN in the same duct. The presence of invasive cancer nearby readily helps establish the diagnosis.

8.6.3 Intravascular Invasion of Pancreatic Ductal Adenocarcinoma

When pancreatic ductal adenocarcinoma invades into vessels it may grow along the luminal surface of the vessel and mimic high-grade PanIN (see Chap. 9, Sect. 9.10 and Figs. 9.35 and 9.36). Elastica van Gieson (EVG) stain may be used to identify the vessel wall, but be aware that the normal pancreatic ductal system also contains elastin fibers in the wall, but not smooth muscle (see Chap. 1, Sect. 1.4.3 and Fig. 1.17). Therefore, when ducts are involved by PanIN (Fig. 8.8), be careful not to mistake this for vascular invasion on EVG stain.

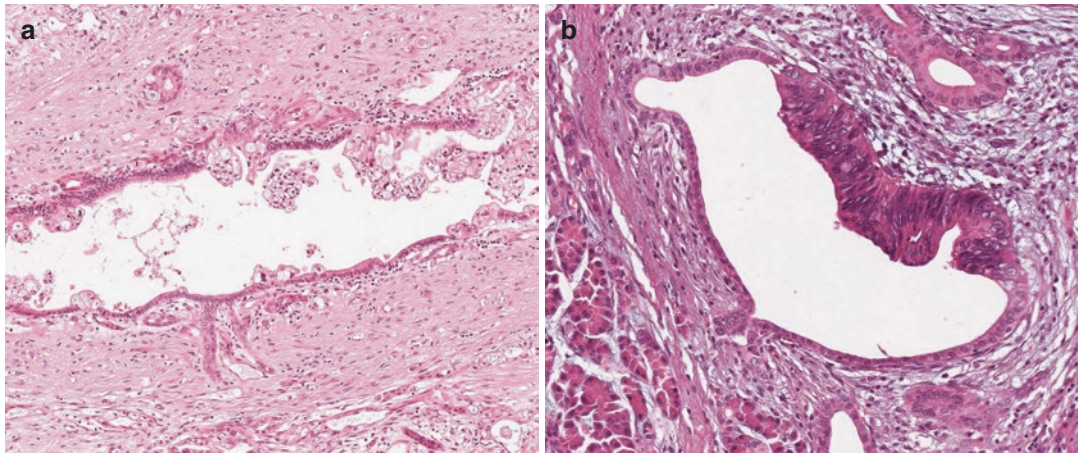

Fig. 8.7 Cancerization of ducts: there is luminal growth along a benign duct by invasive ductal adenocarcinoma (**a**). Duct cancerization may be mistaken for high-grade PanIN (**b**). However, the sharp transition seen here between the highly atypical epithelium and the normal epithelium indicates that this is cancerization

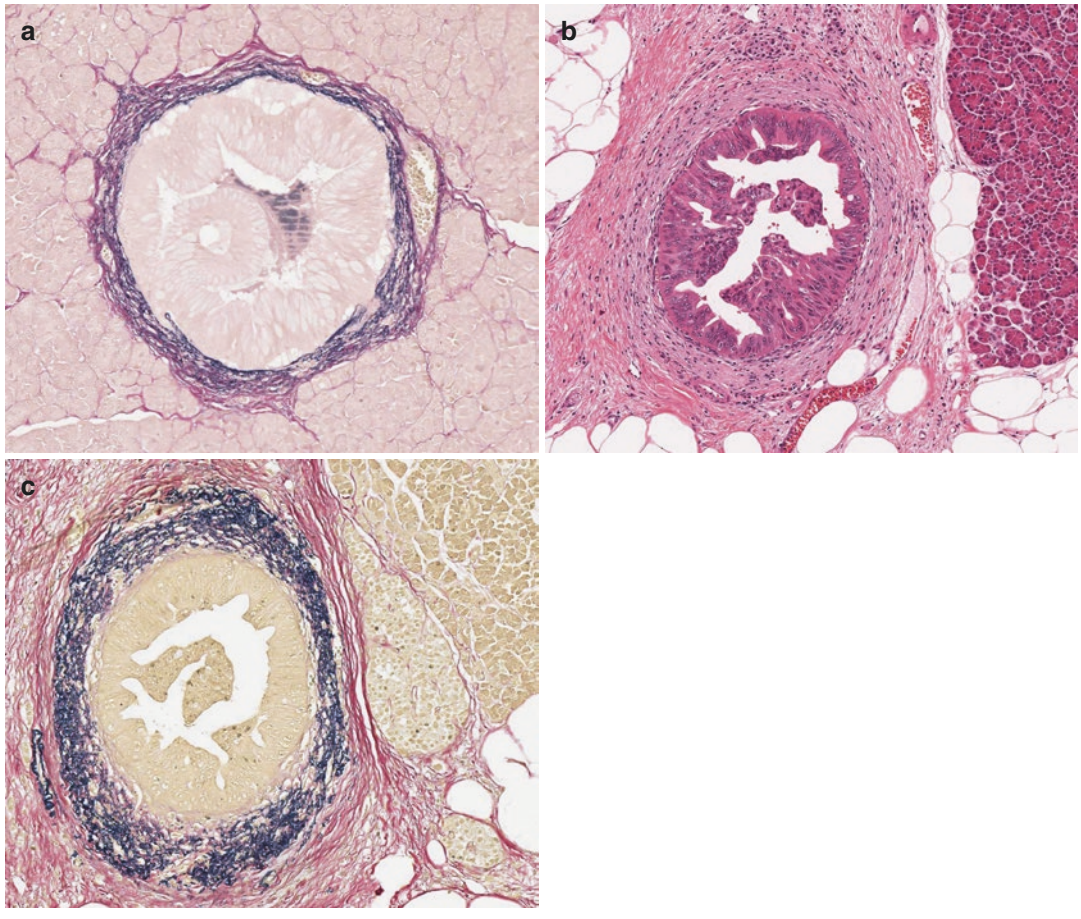

Fig. 8.8 Elastin fibers around PanIN: there are elastin fibers around normal ducts, which may then be involved by low-grade PanIN (**a**). Note the normal acinar tissue around this PanIN. In this example of (**b**) high-grade PanIN (shown at higher power in Fig. 8.4a), the normal periductal elastin fibers (**c**) should not be mistaken for vascular invasion. Elastica van Gieson (EVG) stain

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Further Reading

Basturk O, Esposito I, Fukushima N, Furukawa T, Hong SM, Klöppel G, et al. Pancreatic intraepithelial neoplasia. In: Lokuhetty D, White VA, Watanabe R, Cree IA, editors. Digestive system tumours. WHO classification of tumours 5th edition. Lyon: IARC Press; 2019. p. 307–9.