5 Common Minor Changes

This chapter describes a range of minor changes that can be observed relatively frequently in the pancreas. Most of these alterations are believed to develop in response to physiological changes, mild injury or ageing. The significance of these changes lies therefore in their correct identification and distinction from clinically more relevant lesions. However, recently, a few of these common changes have been implicated in the development of ductal adenocarcinoma of the pancreas, either as a possible risk factor, progenitor lesion, or a sentinel change. The molecular mechanisms underlying the development of these apparently minor changes are currently being actively researched.

5.1 Acinar Cell Nodules

Acinar cell nodules represent an incidental microscopic finding, which is more commonly observed in adults. They are characterized by sharply circumscribed nodules that stand out from the surrounding acinar parenchyma by their divergent tinctorial quality. They can be of an unusually prominent eosinophilic appearance, which is caused by loss of the normal basal basophilia of acinar cells. Less commonly, the acinar cell nodules may exhibit greater cellular basophilia than normal due to an increased nuclear to cytoplasmic ratio and the loss of apical zymogen granules. In addition, the cytoplasm of the lesional cells may be increased, decreased, or occasionally vacuolated; the nuclei may appear hyperchromatic or pyknotic; and the normal polarity of the acinar cells may be lost. Acinar cell nodules range in size from 100 to 1100 μm, and they may occur as solitary or multiple lesions. They have been previously reported under a variety of terms, including focal acinar transformation, eosinophilic degeneration, atypical acinar cell nodule, focal acinar cell dysplasia, or pseudoislet. The latter term refers to the superficial similarity of the less basophilic acinar cell nodules with Langerhans' islets (Fig. 5.1). The etiology and clinical significance—if any—of this lesion are unknown. However, there is no evidence to suggest that acinar nodules represent a neoplastic change.

5.2 Acinar Dilatation

Acinar dilatation (or acinar ectasia) is a common finding in autopsy and surgical material. It may affect a single acinus or multiple acini, sometimes an entire lobule. The dilated acinar lumen may be empty or contain eosinophilic, stringy or occasionally laminated, material. The acinar cells are flattened, the cytoplasm may become homogeneously eosinophilic and the nucleus compressed, such that the affected acinus resembles a ductule (Fig. 5.2). The etiology is poorly understood, and an association with a variety of conditions, including uremia, dehydration, intestinal obstruction, sepsis, congestive heart failure, intracranial lesions, ulcerative colitis, and malignancy, has been described.

F. Campbell, C. S. Verbeke, *Pathology of the Pancreas*,
https://doi.org/10.1007/978-3-030-49848-1_5

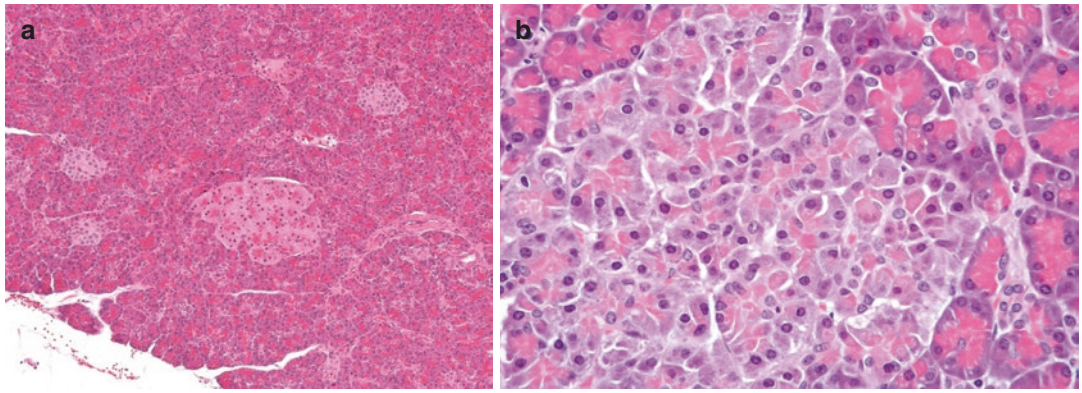

Fig. 5.1 Acinar cell nodule: a sharply circumscribed nodular cluster of acini stands out from the remainder of the acinar parenchyma. Note the superficial resemblance with islets (**a**). The acinar cells are paler and lack the characteristic basophilia at the basal pole of the cytoplasm (**b**)

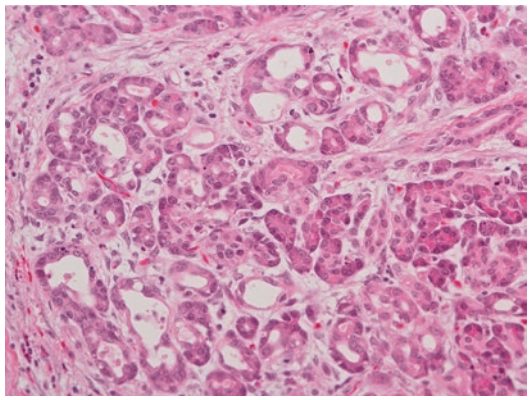

Fig. 5.2 Acinar dilatation: multiple acini within a lobule have a dilated lumen and the lining acinar cells are flattened. A small amount of eosinophilic secretion is present in some of the lumina

The main diagnostic significance of acinar dilatation lies in its distinction from well-differentiated adenocarcinoma, which on occasion is a differential to be considered in small biopsies or on frozen section examination.

5.3 Acinar to Ductal Metaplasia

Acinar cells in the adult pancreas show high plasticity, and under certain circumstances they can undergo transdifferentiation to a cell type with ductal characteristics, a phenomenon called acinar to ductal metaplasia. This alteration is characterized by the dilatation of an acinus (or, more commonly, a cluster of acini) with formation of a duct-like tubular structure that has a clearly visible patent lumen and is lined by flatter epithelial cells. The latter have a phenotype intermediate between acinar and duct-epithelial cells, morphologically and in terms of immunohistochemical marker expression (Fig. 5.3). Acinar to ductal metaplasia is a common and reversible process during acute pancreatitis, and the resulting cells are believed to contribute to the regeneration of acini and repopulation of the pancreas. However, experiments with transgenic mouse models show that acinar to ductal metaplasia may become irreversible when cells acquire oncogenic *Kras* mutations and/or persistent aberrant growth factor signaling, and that these cells may progress to low-grade pancreatic intraepithelial neoplasia (PanIN).

Acinar to ductal metaplasia is often associated with a degree of acinar atrophy and low-grade PanIN of the newly formed, small ducts, and as such it is often part of so-called lobulocentric atrophy (see Sect. 5.5). Acinar to ductal metaplasia is commonly identified in chronic pancreatitis and in resection specimens for ductal adenocarcinoma. Despite its emerging role in pancreatic carcinogenesis in mice, the proof that acinar to ductal metaplasia is linked to the development of human pancreatic cancer, either by preceding the PanIN progression model or through the initiation of dysplastic lesions other than PanIN, is still awaited [1]. Therefore, acinar

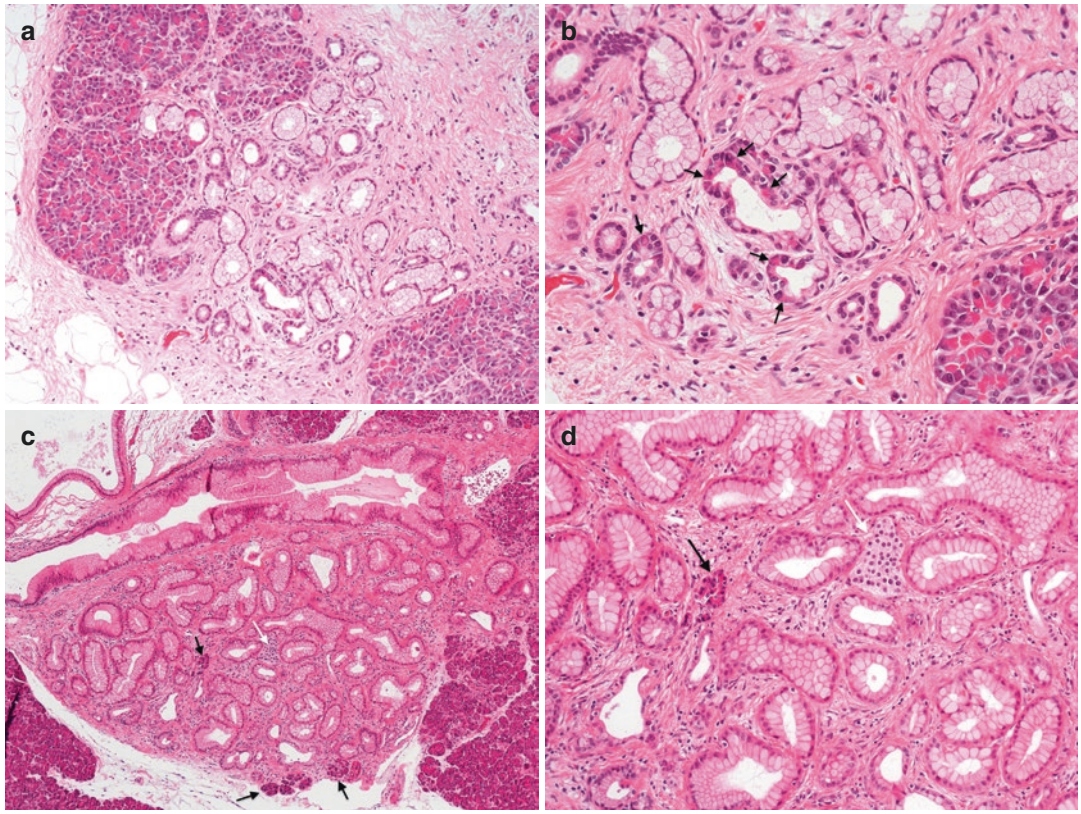

Fig. 5.3 Acinar to ductal metaplasia: some of the acini in this lobule have changed into small ductular structures (**a**). The latter are lined with mucin-rich columnar epithelium, consistent with low-grade PanIN, but some have retained cytoplasmic eosinophilia (*arrows*) (**b**). Almost the entire lobule has undergone acinar to ductal metaplasia, with only a few acini remaining (*black arrows*). Note the presence of a residual islet *(white arrow*) and the extensive low-grade PanIN changes in both the newly formed ductules and the adjacent interlobular duct (**c, d**)

to ductal metaplasia is currently not regarded as a core data item that should be included in diagnostic pathology reports.

5.4 Duct Epithelial Metaplasia

Several forms of metaplasia may affect the duct-lining epithelium (Fig. 5.4).

Squamous metaplasia is a common finding, which can occur anywhere in the pancreatic duct system. It is most commonly associated with chronic pancreatitis, in particular in the presence of intraductal calculi (see Chap. 7, Sect. 7.2.4). *Goblet cell (intestinal) metaplasia* may occasionally be identified as an isolated finding, usually in larger ducts in the vicinity of the ampulla of Vater. Goblet cells may occasionally be part of pancreatic intraepithelial neoplasia (PanIN), in which case the presence of cytological and architectural atypia should allow distinction from a mere metaplastic process (see Chap. 8, Sect. 8.3). *Oncocytic metaplasia* affects centroacinar cells and smaller duct ramifications and can be seen in the context of chronic pancreatitis or in otherwise unremarkable pancreatic tissue.

Probably the most common change exhibited by duct epithelium consists of a higher mucin content associated with a tall columnar cell shape. In the older literature this was reported as mucinous metaplasia or mucinous cell hypertrophy. However, currently it is regarded as a manifestation of low-grade PanIN (see Chap. 8, Sect. 8.2.1).

On rare occasion, in the context of sustained injury and inflammation, the main pancreatic duct

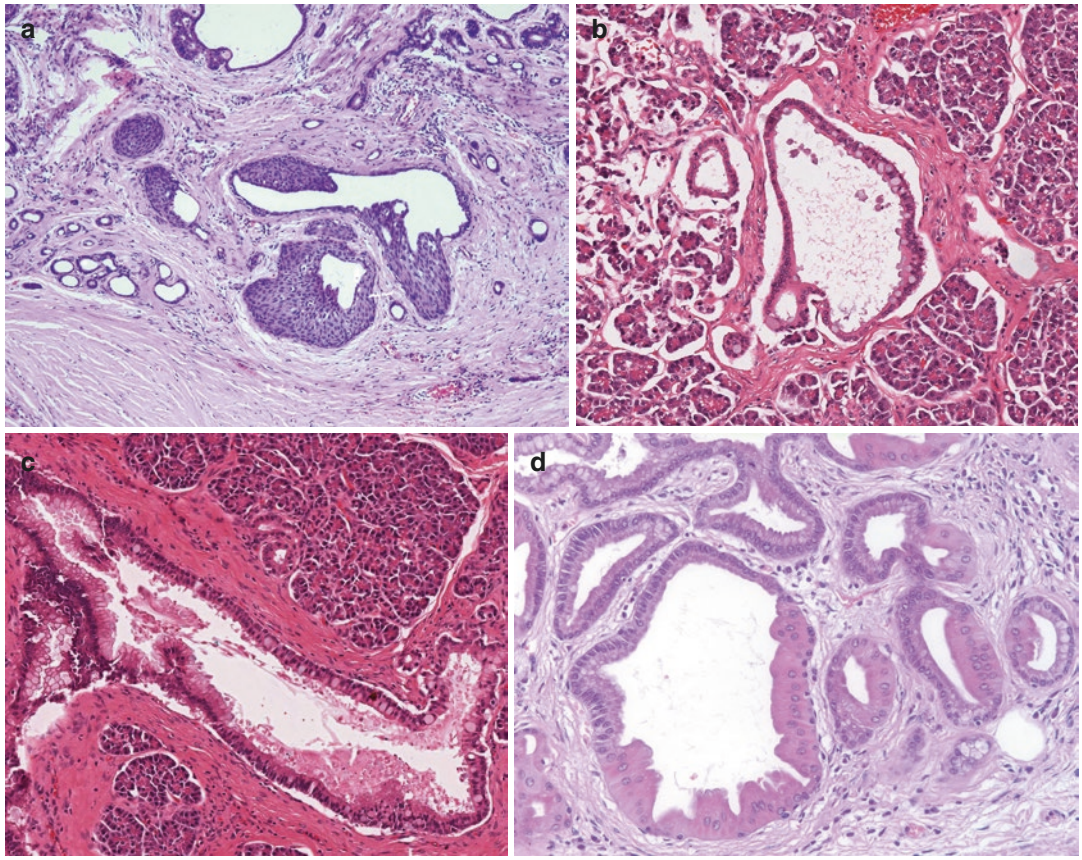

Fig. 5.4 Duct epithelial metaplasia: the lining of a cluster of mildly dilated ducts is replaced by mature squamous epithelium (**a**). Intestinal metaplasia is characterized by the presence of goblet cells within the duct-lining epithelium (**b**). Intestinal metaplasia with goblet cells is seen within an interlobular duct showing low-grade PanIN changes (**c**). In oncocytic metaplasia, the epithelial cells have copious eosinophilic cytoplasm (**d**)

and first-generation, large branch ducts may contain clusters of tightly packed, small glands that are located immediately underneath the surface epithelium. The glands resemble those of the pylorus and are lined with mucinous epithelial cells that are MUC5AC-positive (Fig. 5.5; see also Fig 7.11). These reparative changes are believed to result from hyperplasia of the pancreatic duct glands, i.e., the small blind-ending outpouches that are present in the large ducts of the pancreatic duct system (see Chap. 1, Sect. 1.4.3). While this rare change may at first glance resemble low-grade PanIN, the localization of the glands somewhat deeper below the surface epithelium, the absence of PanIN-like changes in the overlying duct-lining epithelium, and the context of heavy inflammation, will enable distinction from PanIN.

5.5 Lobulocentric Atrophy

Lobulocentric atrophy refers to a combination of changes, including atrophy of acinar parenchyma, acinar to ductal metaplasia, and fibrosis. 'Lobulocentric' indicates that the changes affect the center of the pancreatic lobules. The degree of changes can vary from only partial acinar atrophy with a small focus of acinar to ductal metaplasia to nearly complete acinar atrophy with replacement of most of the affected lobule by acinar to ductal metaplasia, fibrosis, and clustered islets. The changes are usually patchy, such that one lobule can be affected, while a neighboring lobule remains unaltered (Fig. 5.6). Lobulocentric atrophy is often associated with low-grade PanIN of

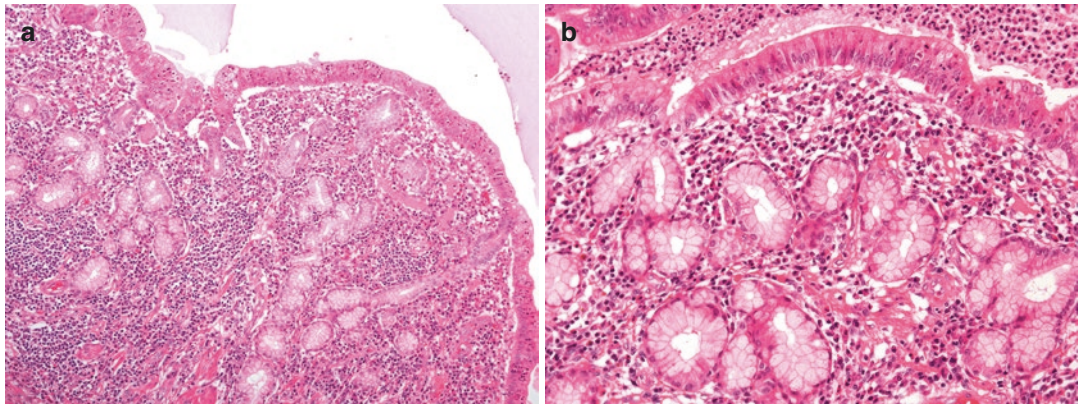

Fig. 5.5 Hyperplasia of periductal glands: the wall of this heavily inflamed main pancreatic duct contains clusters of small glands that are lined with mucinous columnar epithelium and resemble pyloric glands (**a**). In contrast to low-grade PanIN, the surface epithelium is free of PanIN-like changes (**b**). Inflammation in this case was due to actinomyces infection (same specimen as illustrated in Fig. 7.11)

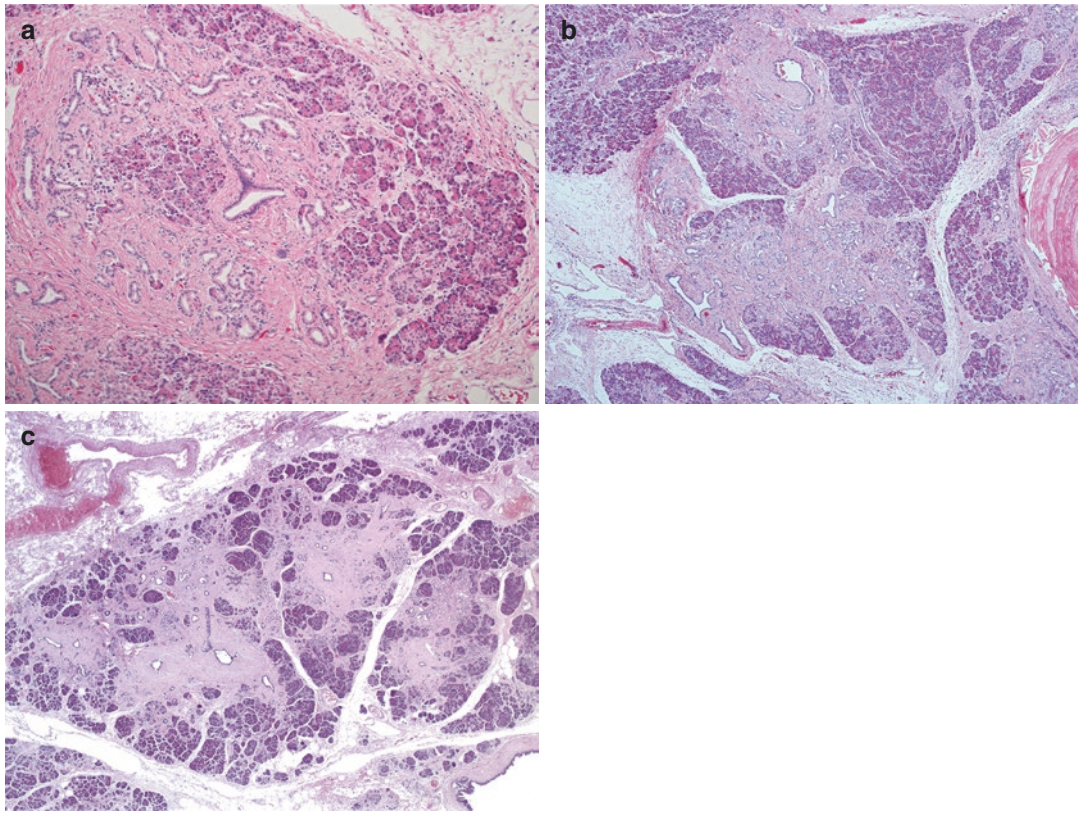

Fig. 5.6 Lobulocentric atrophy: in this lobule, acinar to ductal metaplasia is associated with marked atrophy and fibrosis of the central lobular area (**a**). Similar changes affect several neighboring lobules. Note the rim of residual acini at the periphery of the affected lobules (**b**). Most of the acinar parenchyma in the center of multiple lobules has been effaced and replaced by fibrosis with scattered ducts (**c**)

the intralobular ducts within the affected lobules, but the relationship between lobulocentric atrophy, acinar to ductal metaplasia, and PanIN, and the underlying pathogenetic mechanisms remain unclear. Because lobulocentric atrophy can measure a few millimeters in size and is therefore possibly detectable on endoscopic ultrasound (EUS) investigation, it has been suggested as a surrogate marker for PanIN in individuals who are at a high risk for developing ductal adenocarcinoma of the pancreas (see Chap. 6, Sect. 6.6) [2–4]. However, occurrence of lobulocentric atrophy is not limited to high-risk individuals and may also be found in chronic pancreatitis, in resection specimens with pancreatic ductal adenocarcinoma, in fatty atrophy of the pancreas, and in a variety of other conditions.

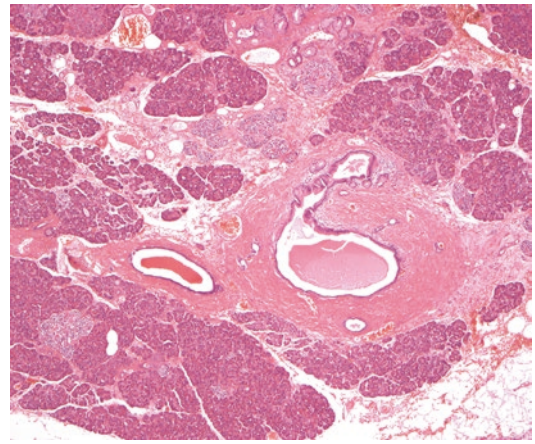

Fig. 5.7 Ageing pancreas: pancreas of a healthy octogenarian with mild duct dilatation and inspissated secretion, discrete periductal and inter-/intralobular fibrosis, as well as focal mild acinar atrophy

5.6 Age-Related Alterations

A range of histological changes in the pancreas has been associated with advancing age. None of these are specific, and similar changes may be seen in a different context. Various studies have shown that the pancreatic volume decreases with age, and concomitant with this change, the pancreatic exocrine function is gradually reduced with age. However, only 5% of otherwise healthy individuals older than 70 years of age develop exocrine pancreatic insufficiency [5]. In contrast, in healthy (non-diabetic) elderly individuals the β-cell mass remains preserved.

Fatty replacement or lipomatosis is increasingly frequent with advancing age (see Sect. 5.7) [6]. Pancreatic fat increases with age until approximately the age of 60, when this process reaches a plateau, while atrophy of the acinar parenchyma continues, resulting in an increased fat/parenchymal ratio in elderly individuals. Probably as a result of parenchymal atrophy and the replacement by adipose or fibrous tissue, lobulation of the pancreatic tissue may become more prominent both on imaging and macroscopic inspection.

Mild focal or segmental *duct ectasia*, of the main pancreatic duct or smaller branch ducts, can also be part of the spectrum of age-related pancreatic changes. Dilatation of the main pancreatic duct to over 4 mm in diameter was found at autopsy in 16% of cases [7]. In addition, small amounts of inspissated secretion may be present in the dilated ducts, and there may be a mild degree of periductal fibrosis (Fig. 5.7). Squamous metaplastic changes of the duct epithelium and low-grade PanIN may be seen (see Chap. 8). Acinar dilatation and prominence of centroacinar cells and intercalated ducts may also be part of the spectrum of alterations. All of these changes are neither strictly defined nor specific for advancing age, and similar alterations may also be seen in association with a variety of conditions and factors, including uremia, duct obstruction of any cause, ductal adenocarcinoma, excessive alcohol consumption, or cigarette smoking. The distinction from changes of early chronic pancreatitis may be difficult on morphological grounds only (see Chap. 7, Sect. 7.2.4).

5.7 Fatty Replacement

Fatty replacement of the pancreas, also known as adipose atrophy or lipomatosis of the pancreas, is a relatively common condition. The presence of adipocytes in the pancreas can vary from the common scattering of a few fat cells to the subto-

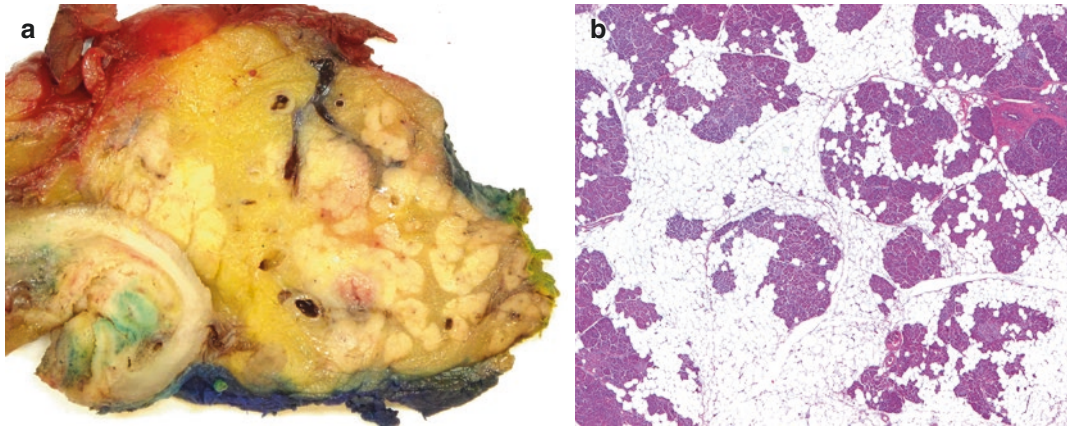

Fig. 5.8 Lipomatosis: the pancreatic lobules are reduced in number and separated by expanses of adipose tissue (**a**). Adipose tissue is present within and in between lobules. The amount of acinar parenchyma is markedly reduced (**b**)

tal replacement of the pancreatic parenchyma by adipose tissue (Fig. 5.8). Adipocytes can be seen within the parenchymal lobules and/or they accumulate in the interlobular space. The islets and ducts usually remain unaffected. While previously regarded as a finding of little if any importance, fatty replacement has recently become the subject of research, because epidemiological studies have shown that fat accumulation in the pancreas (and other viscera) is associated with obesity and type 2 diabetes mellitus, which are known risk factors for pancreatic cancer [8]. The pathophysiological role of the accumulation of adipocytes in the development of pancreatic ductal adenocarcinoma is poorly understood. Animal experiments suggest that through the release of pro-inflammatory and growth-promoting cytokines, adipocytes may promote cancer development and progression [9]. At the same time, obesity could be a risk factor for pancreatic cancer through the association with the development of diabetes mellitus. Meanwhile, a range of other conditions are known to be associated with fatty replacement of the pancreas, including dyslipidemia, arterial hypertension, steatosis of the liver, metabolic syndrome, human immunodeficiency virus-1 infection and/or antiretroviral therapy, and obstruction of the pancreatic duct. On rare occasions, fatty replacement may be seen in the context of cystic fibrosis (see Chap. 6, Sect. 6.1), hereditary pancreatitis (see Chap. 6, Sect. 6.3), Shwachman-Diamond syndrome, or Johanson-Blizzard syndrome, but these patients may present with clinical signs and symptoms of exocrine insufficiency. The clinical implications of fatty replacement are currently not clear and diagnostic criteria are lacking, both for radiological and histological diagnosis [10].

Fatty replacement of the pancreas is usually a diffuse process, although the degree of the fatty change may vary at the microscopic level. Occasionally, fatty replacement may appear as a single, focal, well-circumscribed lesion that is surrounded by normal pancreatic parenchyma, does not cause deformation of the organ countours, and may be difficult to correctly diagnose on preoperative imaging (Fig. 5.9).

5.8 Changes in Islets

The presence of endocrine cells within pancreatic ducts, often referred to as *ductulo-insular complexes* (see Chap.1, Sect. 1.4.4) can be seen in the context of chronic pancreatitis or endocrine cell hyperplasia (see Chaps. 7 and 21, Sects. 7.2.4 and 21.1).

Deposition of *amyloid* within islets may occur in older individuals, in particular in patients with type 2 insulin-independent diabetes mellitus (Fig. 5.10). There is no association between islet and systemic amyloidosis. Hyaline fibrosis

of islets, for example, in the context of chronic pancreatitis, may mimic islet amyloidosis, but distinction can easily be made with the help of a Congo red stain.

Cystic dilatation of islets is sometimes encountered in normal pancreatic tissue or in resection specimens for pancreatic cancer. It is of no known clinical significance, and the cause of the dilatation is usually not identifiable. The resulting cyst is an incidental microscopic finding, as the cyst diameter rarely exceeds 1–2 mm. The wall of the cyst is lined with endocrine cells, which in some areas may appear flattened. Immunostaining for chromogranin or synaptophysin can easily demonstrate the endocrine nature of this lesion (Fig. 5.11), which is helpful in distinguishing it from a small acinar cystic transformation (acinar cell cystadenoma), with which it may share superficial similarity (see Chap. 19, Sect. 19.1).

Focal reactive endocrine cell hyperplasia, a common finding in the context of acinar atrophy, is described in Chap. 21, Sect. 21.1.

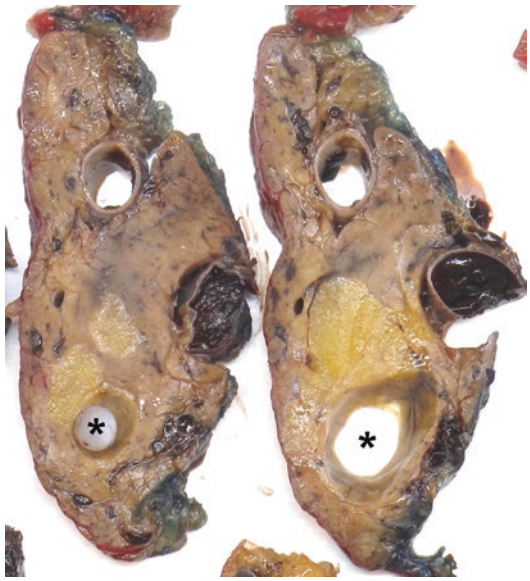

Fig. 5.9 Segmental fatty replacement: a sharply circumscribed area of fatty replacement is surrounded by unremarkable pancreatic parenchyma. Note the presence of a retention cyst (*asterisk*)

5.9 Autolytic Change

Pancreatic tissue is susceptible to autolytic change, and affected parenchymal areas may vary in extent from small randomly scattered foci to large expanses, in which case microscopic examination may be hampered (Fig. 5.12). Autolytic change should not be misinterpreted as genuine tissue necrosis, from which it can be distinguished first and foremost by the absence of an inflammatory reaction, that is, infiltration of leukocytes.

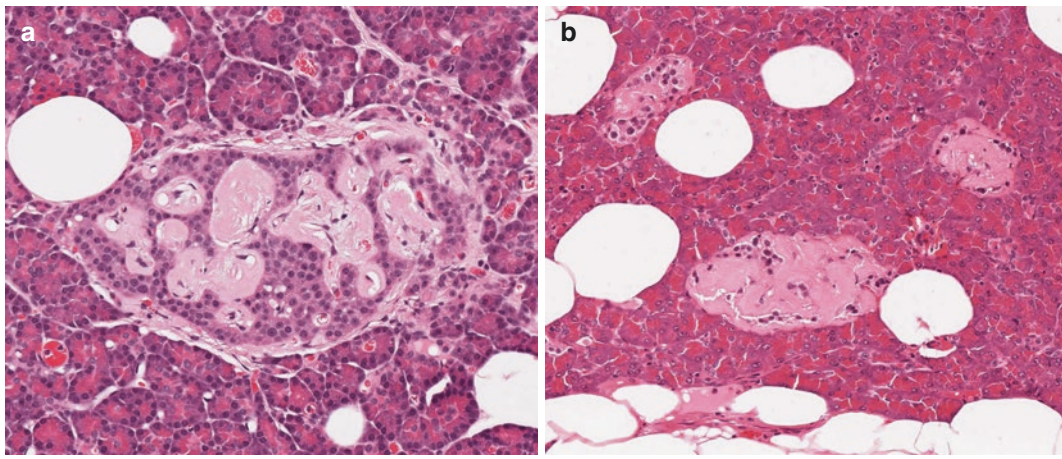

Fig. 5.10. Islet amyloidosis: extracellular deposits of amorphous eosinophilic material expand the space between islet cells (**a**). Several islets are nearly obliterated by amyloid deposits (**b**)

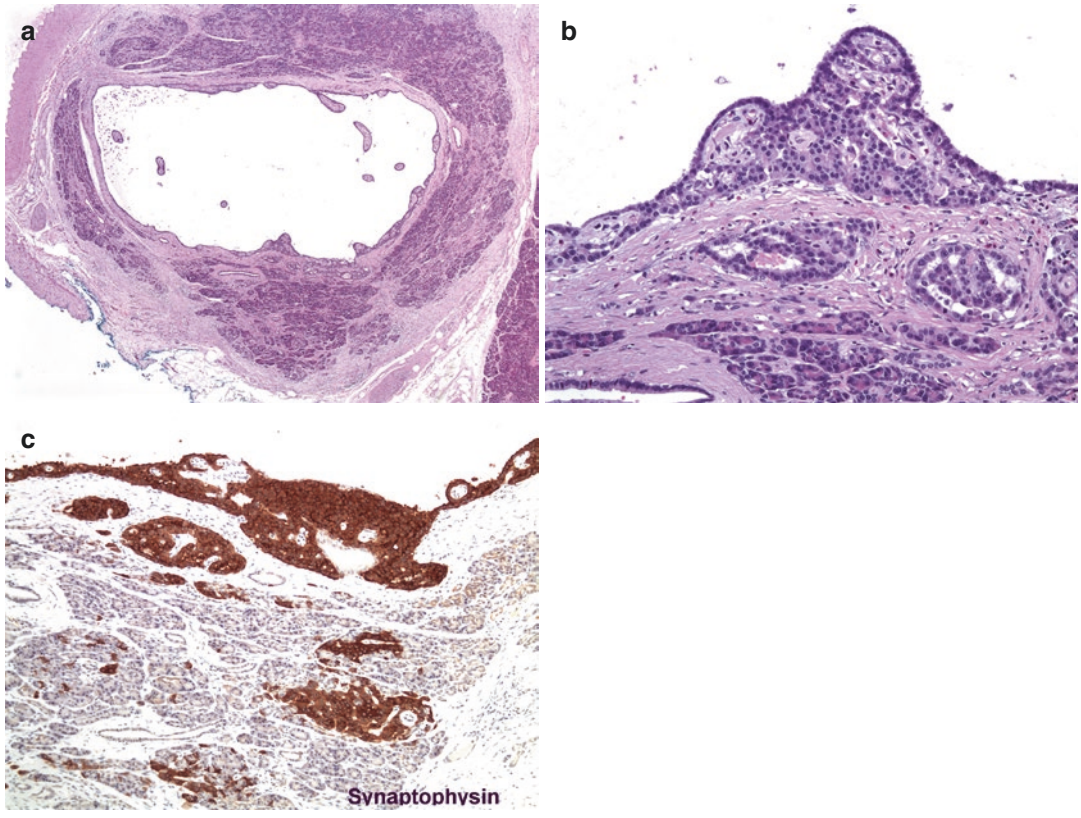

Fig. 5.11 Cystic islet dilatation: a small simple cystic space within an otherwise intact lobule (**a**) is surrounded by unremarkable islet cells (**b**) showing positive immunostaining for synaptophysin (**c**)

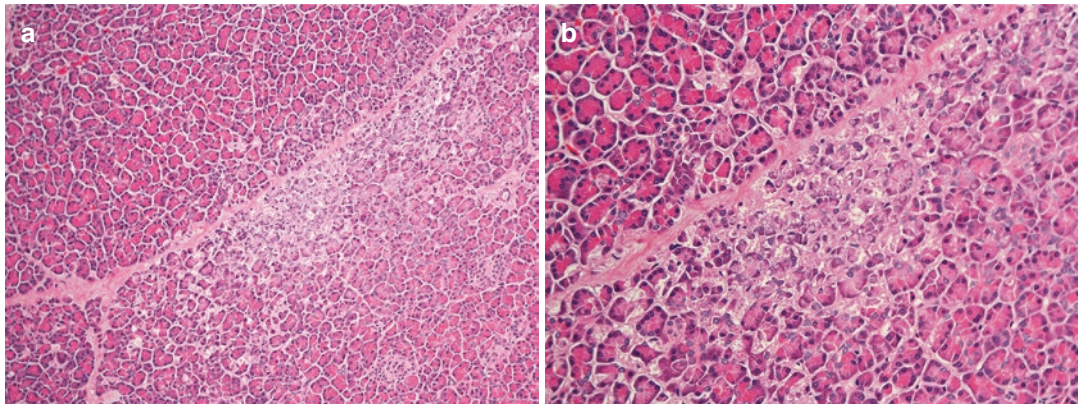

Fig. 5.12 Artefact mimicking necrosis: foci of acinar parenchyma of varying size and random localization show loss of normal cellular structures and staining (**a**). The absence of an inflammatory response distinguishes this artefactual change from necrosis, with which it bears superficial resemblance (**b**)

References

1. Storz P. Acinar cell plasticity and development of pancreatic ductal adenocarcinoma. Nat Rev Gastroenterol Hepatol. 2017;14:296–304.
2. Brune K, Abe T, Canto M, O'Malley L, Klein AP, Maitra A, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. Am J Surg Pathol. 2006;30:1067–76.
3. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. Arch Pathol Lab Med. 2009;133:365–74.
4. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020;69:7–17.
5. Löhr J-M, Panic N, Vujasinovic M, Verbeke CS. The ageing pancreas: a systematic review of the evidence and analysis of the consequences. J Intern Med. 2018;283:446–60.
6. Matsuda Y. Age-related morphological changes in the pancreas and their association with pancreatic carcinogenesis. Pathol Int. 2019;69:45062.
7. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol. 1984;15:677–83.
8. Sreedhar UL, DeSouza SV, Park B, Petrov MS. A systematic review of intra-pancreatic fat deposition and pancreatic carcinogenesis. J Gastrointest Surg. 2019 Nov 20. https://doi.org/10.1007/s11605-019-04417-4. [Epub ahead of print]
9. Chang H-H, Eibl G. Obesity-induced adipose tissue inflammation as a strong promotional factor for pancreatic ductal adenocarcinoma. Cells. 2019;8:673.
10. Khoury T, Asombang AW, Berzin TM, Cohen J, Pleskow DK, Mizrahi M. The clinical implications of fatty pancreas: a concise review. Dig Dis Sci. 2017;62:2658–67.