HHS Public Access

Author manuscript

Surg Pathol Clin. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Surg Pathol Clin. 2016 December ; 9(4): 619–641. doi:10.1016/j.path.2016.05.007.

BENIGN TUMORS AND TUMOR-LIKE LESIONS OF THE PANCREAS

Olca Basturk, MD[1] and **Gokce Askan, MD**[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY

Synopsis

The pancreas is a complex organ that may give rise to large number of neoplasms and non-neoplastic lesions. This article will focus on benign neoplasms such as serous neoplasms as well as tumor-like (pseudotumoral) lesions that may be mistaken for neoplasm not only by clinicians and radiologists, but also by pathologists. The family of pancreatic pseudotumors, by a loosely defined conception of that term, includes a variety of lesions including heterotopia, hamartoma, and lipomatous pseudohypertrophy. Autoimmue pancreatitis (covered in chronic pancreatitis chapter) and paraduodenal ("groove") pancreatitis may also lead to pseudotumor formation. Knowledge of these entities will help in making an accurate diagnosis.

Keywords

Benign; serous; lymphoepithelial; squamoid; epidermoid; hamartoma; inflammatory; pancreatitis

SEROUS NEOPLASMS

Serous neoplasms of the pancreas are rare benign tumors accounting for approximately 1% of all pancreatic lesions. These tumors reveal a unique cytomorphology characterized by distinctive cuboidal epithelial cells with uniform round nuclei, dense, homogenous chromatin, and a prominent epithelium-associated microvascular meshwork [1, 2]. They are generally regarded under the category of ductal-type tumors; however, they do not produce mucin despite their presumed ductal lineage, instead, they produce abundant glycogen.

Several morphologic variants of serous neoplasms have been described. These include *microcystic* and *macrocystic (a.k.a. oligocystic)* serous cystadenomas, solid serous adenoma, and von Hippel-Lindau (vHL)-associated serous cystic neoplasm. The *microcystic* serous cystic neoplasm consists of innumerable small, irregularly contoured tubular structures of variable shapes, the vast majority of which measure in submillimeters. The *macrocystic (oligocystic)* serous cystic neoplasms are predominantly or completely composed of fewer (typically less than 10) but much larger cysts, each measuring in centimeters. Although "serous cystadenoma (SCA)" and "serous cystic neoplasm (SCN)" terms technically refer to

Corresponding Author: Olca Basturk, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, basturko@mskcc.org.

Disclosure

The authors have no conflict of interest to declare.

the *microcystic* variant; they are often used interchangeably for both microcystic and macrocystic variants. Solid serous adenoma is characterized by uniform, small, evenly shaped and sized nests or tubules with minimal or no lumen formation [1]. vHL-associated serous cystic neoplasms are often more a patchy transformation in the pancreas, although some may form a well-defined localized mass [3–8].

Microcystic and Macrocystic (Oligocystic) Serous Cystadenomas

Serous cystadenomas can occur at any age but it is more common in elderly female patients [1, 7–21]. They are often asymptomatic [11, 22, 23], discovered incidentally, either sporadically or as part of vHL disease [7, 8, 24–27]. If the mass is located in the pancreatic head, it can obstruct the biliary tract [25, 28]. Rarely, the lesions are multiple, specifically when associated with vHL.

A “honeycomb” appearance on CT or MRI, associated with a central scar that may or may not be calcified, is characteristic for *microcystic* variant [16, 17, 22, 29–31]. However, the diagnosis is often not accomplished preoperatively by imaging studies. Similarly, *macrocystic (oligocystic)* variant, especially if only a single cyst is evident [32], radiographically simulates intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and pseudocysts [16, 19, 30, 33–35].

The FNA diagnosis of serous neoplasms has also proven to be unexpectedly challenging because of the very low aspirate cellularity, probably due to the cohesiveness and adhesion of the cells to the tissue [1, 36–38]. The tumor cells are bland, cuboidal, and arranged in loose clusters or monolayers. The cytoplasm is usually cleared or vacuolated. However, the cells are frequently stripped of cytoplasm, showing only small, round nuclei with fine but dense, homogenous nuclear chromatin [31, 36, 39].

The presurgical diagnosis of pancreatic cysts has traditionally relied on measuring cyst fluid amylase as well as the tumor markers CA19-9 and CEA to identify and distinguish the mucinous neoplasms from non-mucinous lesions such as serous neoplasms [40]. However, the sensitivity and specificity of these markers are relatively low [41]. Recently, in an ELISA analysis of cyst fluid and tumoral tissue, Yip-Schneider et al. found that vascular endothelial growth factor-A (VEGF-A) was markedly elevated in serous cystic neoplasms when compared to pseudocysts, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and pancreatic ductal adenocarcinoma [42]. With a cut off of 8500pg/mL, VEGF-A had 100% sensitivity and 97% specificity as a marker of serous cystic neoplasms, making it a very promising biomarker for the diagnosis and distinction of serous cystic neoplasms from other pancreatic cysts, particularly when used in conjunction with CEA [42].

Similarly, the identification of cyst-specific somatic mutations (involving *KRAS, GNAS, RNF43, CTNNB1,* and *VHL* genes) offers great promise in the presurgical diagnosis of pancreatic cysts. Recently, *KRAS* and *GNAS* mutations have been shown to have 96% sensitivity and 100% specificity for the differentiation of intraductal papillary mucinous neoplasm from serous cystic neoplasm [41]. Molecular assays containing a 5-gene panel may be especially useful in the pretreatment diagnosis of serous cystic neoplasms since isolated *VHL* mutations have not been identified in intraductal papillary mucinous neoplasms and

mucinous cystic neoplasms. However, it should be kept in mind that pancreatic neuroendocrine tumors may also be cystic and may harbor *VHL* deletions in up to 25% of sporadic cases.

These new developments seem to be very promising for the preoperative diagnosis (and thus possible conservative management) of serous cystic neoplasms; however, they need to be verified in larger-scale studies before they can be put into daily clinical management.

The mean diameter of serous cystic neoplasms is approximately 4 cm but now smaller lesions are found using improved imaging techniques [1, 9, 10]. They occur anywhere in the organ and appear as circumscribed and well-demarcated from the surrounding pancreas. *Microcystic* serous cystic neoplasms form partly encapsulated, lobulated masses composed of innumerable tiny cysts, which impart the highly distinctive and entity-defining sponge-like appearance on sectioning (Figure 1). Irregular central scars, frequently calcified, may be seen in the larger tumors. The fluid in the cysts is clear and watery, appearing colorless, yellow, or blood stained. Foci of hemorrhage can occur [43]. *Macrocystic (oligocystic)* serous cystic neoplasms, by definition, are composed of much larger cysts with fewer loculi and devoid of central fibrosis or calcification (Figure 2).

Microscopic examination of *microcystic* serous cystic neoplasms reveal back to-back tubules of variable size and shape (Figure 3), creating a characteristic *microcystic* pattern formed by cuboidal epithelium. Scattered larger (up to a centimeter in diameter), more irregular cysts lined by low cuboidal to flat cells may also be seen [7, 15, 17, 19–21, 44]. Dense stroma can occur in the lesions with these larger cysts. Some of the stroma may be hyalinized or myxoid. The tumor cells usually have abundant clear cytoplasm due to abundant glycogen (Figure 4). Some cases reveal more oncocytoid cells with granular cytoplasm. Nuclei are small, round, compact, and uniform, with inconspicuous nucleoli. The presence of a capillary meshwork immediately adjacent to (almost within) the epithelium is highly characteristic [45, 46], and has been noted as a striking analogy with other clear cell tumors arising in association with vHL, including renal cell carcinomas and hemangioblastomas [45]. *Macrocystic (oligocystic)* serous cystic neoplasms may be missing much of its lining, thus requiring multiple sections to find the epithelium. The lining of the cysts display the characteristic serous cytology (Figure 5).

Serous cystic neoplasms often show degenerative changes (hemorrhage, inflammation, and cholesterol clefts). Calcifications, tufting/micropapillae (Figure 6), the presence of satellite nodules, and, frequent intermixing of neuroendocrine cell proliferation in a pseudoinvasive pattern are also common [1].

Both histologically and immunophenotypically, these neoplasms appear to recapitulate centroacinar cells [18, 46–48]. The glycogen rich cytoplasm is typically PAS positive, diastase sensitive, and reacts with broad-spectrum and low-molecular-weight keratins, EMA, and inhibin [15, 49]. Ductal mucin markers (B72.3, CA19-9, CEA and MUC1) are either negative or only focally positive, although MUC6 is usually positive [49]. Molecules implicated in clear cell tumorigenesis [glucose uptake and transporter-1 (GLUT-1), hypoxia-inducible factor-1α (HIF-1α), and carbonic anhydrase IX (CA-IX)] are also consistently expressed [45].

At a molecular level, *VHL* gene allelic deletions (chromosome 3p) are detected in serous cystic neoplasms from patients with vHL, providing molecular evidence of their neoplastic nature and integral association with vHL disease [6–8]. However, *VHL* gene alterations may also be detected in sporadic cases [50]. To date, the genetic alterations seen in pancreatic ductal adenocarcinoma (*TP53, KRAS, SMAD4,* and *p16/CDKN2A*), neuroendocrine tumors (*MEN1, DAXX,* and *ATRX*), and intraductal papillary mucinous neoplasms (*GNAS, RNF43, PIK3CA,* and *STK11/LKB1*) have not been reported in serous neoplasms [41, 50].

Serous cystic neoplasms are very slow-growing tumors [9, 51], with an estimated doubling time of 12 years [52]. Therefore, if a definitive diagnosis can be accomplished, watchful waiting is a distinct option for smaller tumors [9, 11, 14, 25, 44, 52–54]. For symptomatic cases and/or larger ones, surgical removal is still the treatment of choice [44, 55]. More recently, radiofrequency ablation, ethanol, and chemotherapeutic agent injection have been proposed as options in the non-surgical management of patients with limited disease [56, 57].

The 2010 WHO classification requires the presence of distant metastasis as the criterion for “malignancy” in serous cystic neoplasm. Thus, many of the cases that had been reported as “malignant” based on “vascular invasion” would no longer qualify by the WHO classification [58]. Similarly, larger serous neoplasms (>11.0 cm) with inflammation and hemorrhage may show localized adhesion and/or penetration of neighboring organs, including lymph nodes, spleen, stomach, and colon, which does not seem to be an indicator of malignant behavior. Even for serous neoplasms occurring in the liver, the possibility of synchronous independent tumors may have to be considered before concluding metastasis, especially considering there was no fatality related to this and no reported metastases to other remote sites [1, 9]. Of note, there are isolated cases reported in which a cytologically obvious carcinoma arose within a microcystic serous cystadenoma (“carcinoma *ex* microcystic adenoma”) [59]. The biological behavior of these rare cases is yet to be defined.

Solid Serous Adenoma

Solid serous tumors with uniform, small, evenly shaped and sized nests or tubules with minimal or no lumen formation has also been described. These typically lack central fibrosis and often misinterpreted radiologically as neuroendocrine tumors. Tumor cells reveal typical glycogen-laden clear cytoplasm and bland, round to oval hyperchromatic nuclei [60–64]. Distinguishing solid serous adenomas from other solid neoplasms, such as neuroendocrine tumors, or other clear-cell neoplasms, such as metastatic renal cell carcinoma, may be difficult; even more so in the setting of vHL, where both lesions may be concurrently present. Special studies and immunohistochemical analysis are helpful [65].

Serous Cystic Neoplasm Key Features Box

Clinical

- Present with nonspecific symptoms or detected incidentally
- Have well-established association with von Hippel-Lindau syndrome
- Molecular assays containing a 5-gene panel (*KRAS, GNAS, RNF43, CTNNB1,* and *VHL* genes) may be useful in the pretreatment diagnosis

Macroscopic

- Medium size lesion (mean size = 4 cm)
- Well-demarcated and sponge-like appearance with innumerable small cysts, each measuring a few millimeters is diagnostic
- Central stellate scar common in *microcytic* variant

Microscopic

- Conglomerate of cysts lined by simple cuboidal epithelium
- Clear or eosinophilic cells with distinct cytoplasmic borders
- Small, round nuclei with dense, homogenous chromatin
- Similar to vHL syndrome-associated other clear cell tumors, a prominent epithelium-associated microvascular meshwork is present

INFLAMMATORY MYOFIBROBLASTIC TUMOR

Inflammatory myofibroblastic tumor is a rare, especially in the pancreas, and distinctive entity [66–69]. The pancreatic head is affected most frequently by an ill defined and firm mass causing obstructive jaundice. Therefore, patients are often suspected to suffer from pancreatic ductal adenocarcinoma [70, 71].

At low-power-magnification, inflammatory myofibroblastic tumor has a relatively pushing border (Figure 7). Fibroblasts and myofibroblasts, usually arranged in a storiform pattern, with moderate to marked inflammation composed of lymphocytes and plasma cells are characteristic (Figure 8). Cytologic atypia and mitotic figures are rarely observed.

In approximately 50% of inflammatory myofibroblastic tumors, various gene aberrations including the anaplastic lymphoma kinase (*ALK*) gene at chromosome 2p23, leading to aberrant ALK expression in the myofibroblasts, have been identified [72–75]. These observations have led to the development of the concept of inflammatory myofibroblastic tumor as a clonal neoplastic lesion rather than a reactive process [69]. Of note, *ALK* gene abnormality is more often seen in children or young adults than in elderly people [67].

Inflammatory myofibroblastic tumors share, at least focally, the morphologic appearance of the IgG4-related sclerosing disease (discussed separately in this issue, see autoimmune pancreatitis section), particularly at areas with prominent fibroblastic/myofibroblastic proliferation mingled with lymphocytes and plasma cells [69, 76]. However, the majority of inflammatory myofibroblastic tumors are different from IgG4-related lesions in terms of the ALK expression, low-level of IgG4+ cell infiltration and lack of obstructive phlebitis. Thus, inflammatory myofibroblastic tumor should be recognized to be a distinctive neoplastic entity [69].

Inflammatory Myofibroblastic Tumor Key Features Box

- Composed of fibroblasts and myofibroblasts, usually arranged in a storiform pattern, with moderate to marked inflammation
- In half of inflammatory myofibroblastic tumors, various *ALK* gene abnormalities, leading to aberrant ALK expression in the myofibroblasts, have been identified
- ALK expression and low-level of IgG4+ cell infiltration help distinguishing inflammatory myofibroblastic tumors from IgG4-related sclerosing disease

LYMPHOEPITHELIAL CYST

Lymphoepithelial cyst is usually asymptomatic, with the lesion found incidentally on imaging studies performed for unrelated reasons or at autopsy [77, 78]. In contrast with its salivary gland analogues, no autoimmune disorder is identified and there is no syndrome association. Association with HIV also appears to be coincidental and exceedingly uncommon [79].

It typically present as a unilocular or multilocular cyst within, or protruding from, the pancreas. Imaging studies cannot consistently separate lymphoepithelial cyst from neoplastic mucinous cysts, such as intraductal pancreatic mucinous neoplasm or mucinous cystic neoplasm [80]. Fine needle aspiration can support the diagnosis of a lymphoepithelial cyst when squamous cells, amorphous keratinaceous debris, cholesterol clefts and/or lymphocytes are present [81]. However, fine needle aspiration may be inconclusive. Using cyst fluid CEA as a discriminating test has its limitations as several case reports have noted elevated levels of CA19-9 and/or CEA in lymphoepithelial cysts [82–84].

Gross examination shows a medium size (mean size = 5 cm), encapsulated cystic lesion. Depending on the degree of keratin formation, cyst content may vary from serous to cheesy/casseous-appearing. Microscopically, there is a dense band of mature lymphoid tissue with prominent, well-formed germinal centers subtending a cyst lining of mature stratified squamous epithelium occasionally containing keratinaceous debris (Figure 9). The adjacent pancreas may have granulomas, collections of foamy histiocytes and fat necrosis [77, 78] (Figure 10).

Although lymphoepithelial cysts might contain sebaceous glands, they are distinct from dermoid cysts (cystic monodermal teratomas) or teratomas because of the large amount of organized lymphoid tissue present and the lack of hair, cartilage, and occasionally neural tissue [77, 85].

Pancreatic lymphoepithelial cyst can be cured by conservative resection but if it is asymptomatic and diagnosed before surgery, no treatment is necessary. Neither malignant transformation nor recurrence after resection has been reported [86].

Lymphoepithelial Cyst Key Features Box

Clinical

- Mostly in male patients
- Medium size, peripancreatic cyst

Microscopic

- Has variable lining ranging from attenuated to transitional to stratified squamous epithelium with keratinization
- Goblet cells or scanty sebaceous elements may be seen
- Distinct band of lymphoid tissue, sometimes with prominent, well-formed germinal centers, composed of mature T lymphocytes surrounds the epithelium

EPIDERMOID CYST IN INTRAPANCREATIC ACCESSORY SPLEEN

These are very rare lesions seen in younger adults (2nd to 3rd decades). They occur almost exclusively in the tail of the pancreas where accessory spleens are not uncommon. Of note, accessory spleens are most frequently found at the perihilar region of the spleen (80% of cases) followed by the pancreatic tail [87].

Similar with lymphoepithelial cyst, epidermoid cyst in intrapancreatic accessory spleen can also be misdiagnosed preoperatively as a cystic pancreatic neoplasm, such as intraductal papillary mucinous neoplasm or mucinous cystic neoplasm, especially in the setting of elevated serum CA19-9 levels [88, 89].

Grossly, a well-circumscribed dark red mass with a unilocular or multilocular cyst in the pancreatic tail is characteristic [88]. The cyst contains serous fluid or keratinaceous debris and is lined by benign multilayered epithelium, which is reminiscent of squamous epithelium or urothelium, surrounded by unremarkable splenic tissue [78, 88162]. The lining epithelium shows stratified cuboidal or columnar cell morphology in some areas, whereas it is flattened and attenuated in other areas (Figure 11) [159].

SQUAMOID CYST OF PANCREATIC DUCTS

Squamoid cysts of pancreatic ducts are relatively small cysts, with a median size of 1.5 cm, and the vast majority of the cases are detected during work-up for other conditions [90, 91]. These cysts typically result from unilocular cystic dilatation of the ducts and have variable lining ranging from attenuated, flat, non-stratified squamous, to transitional, to mucosal-type stratified squamous epithelium (Figure 12) as well as mucoproteinaceous acidophilic secretions within the lumen. The wall of the cyst is composed of a thin band of fibrous tissue, focally showing tributary ducts. Neither acute nor chronic inflammation is a feature of this lesion.

Immunohistochemically, nuclear p63 expression is present in all cases, a finding that is not seen in any normal component of pancreas or in non-squamous cystic lesions of this organ [92].

It is important to distinguish squamoid cysts of pancreatic ducts from other cystic lesions, in particular, from mucinous tumors, since the latter often have malignant potential, whereas squamoid cysts of pancreatic ducts are innocuous lesions [93]. Preoperative differential diagnosis of these may be difficult, especially in the setting of elevated fluid CEA levels and acellular cytology [94, 95]. However, their distinction at the microscopic level is fairly straight forward [90].

Squamoid Cyst of Pancreatic Ducts Key Features Box

Clinical

- Usually small, unilocular cyst
- Some might undergo resection with the clinical impression of being an intraductal papillary mucinous neoplasm

Microscopic

- Has variable lining ranging from attenuated to transitional to stratified squamous epithelium
- Contains distinctive mucoproteinaceous acidophilic secretions
- The wall is composed of thin fibrous tissue devoid of any lymphoid tissue
- Nuclear p63 expression confirms the nature of the lining

HETEROTOPIC PANCREAS

Heterotopic (ectopic) pancreatic tissue, independent from the vascular supply or anatomic connection to the pancreas, may occur from displacement of small amounts of pancreas during embryologic development [96–98]. It is located most frequently in the stomach and proximal small intestine (Figure 13), but can be identified in other organs such as esophagus, gallbladder, hepatic or common bile ducts, spleen as well as in Meckel diverticulum [99–101].

Depending on the size, location and the pathological changes similar to those observed in case of the normal pancreas, patients may present with symptoms such as epigastric pain, nausea, vomiting, ulcer, obstruction, and weight loss. However, it is often an incidental finding. Radiographically or endoscopically, it may be a challenge to differentiate it from a neoplasm [102, 103].

If it is large enough to be seen on gross inspection, it appears as a firm, pale, nodular mass. Microscopically, it has been classified into three types according to the histologic components (Heinrich classification). Type I is composed of complete structures consisting of ducts, acini, and islets of Langerhans cells (Figure 13). Type II is composed of ducts and acini. Type III is composed of ducts alone [104]. Histologic type is not related to the clinical

symptoms [105]. Of note, small collections of acinar cells in other organs such as gastroesophageal region are regarded as metaplasia rather than heterotopia [106].

In symptomatic cases, surgical excision relieves symptoms. However, rarely, a more extensive treatment may be necessary due to secondary pancreatic neoplasms including adenocarcinomas arising within ectopic pancreatic tissue [101, 107–112].

Heterotopic Pancreas Key Features Box

Clinical

- Occurs in a variety of organs; most common in gastrointestinal tract
- Usually an incidental finding
- May rarely cause symptoms due to local complications or secondary pancreatic pathology

Microscopic

- Components of the pancreas (acini, ducts or islets) in different combinations

PANCREATIC HAMARTOMA

The term hamartoma refers to a focal overgrowth of cells and tissues native to the organ in which it occurs. Thus, hamartoma is regarded as a malformation rather than a true neoplasm [96, 113].

Pancreatic hamartoma is rare, accounting for less than 1% of occurrences of tumor-like lesions [114]. Usually presents as a well-demarcated, solid or solid and cystic mass. It is often located in the head of the pancreas [115–119]. Cases with multiple lesions have been reported [115, 116].

Microscopically, it is characterized by small to medium-sized ductal structures, lined by columnar epithelium without atypia, surrounded by disarranged acini and reveals various amounts of fibrous stroma (Figure 14). Well-formed islets of Langerhans are not common. In fact, Pauser et al. [118, 120] and Yamaguchi et al. [121] defined the criteria for the diagnosis of pancreatic hamartoma as: (1) forming a well-demarcated mass, (2) being comprised of mature acini and ducts with distorted architecture, and (3) lacking discrete islets of Langerhans. Adjacent pancreatic parenchyma is usually unremarkable.

Immunohistochemically, both acinar cells and ductal cells are positive for epithelial markers (AE1/AE3, CAM5.2, and EMA), and the acinar cells are positive for exocrine markers (trypsin, chymotrypsin, etc), similar to what is observed in a normal pancreas. The stromal spindle cells reportedly express CD34 and CD117 but are usually negative for S100, SMA, desmin, and bcl-2 [116–121].

Although pancreatic hamartoma is usually not aggressive, it typically requires surgical resection because of the difficulty in prospective clinical imaging diagnosis [122–124].

NESIDIOBLASTOSIS

Nesidioblastosis is a descriptor of the morphologic changes seen in functional disorders of the endocrine pancreas, characterized by persistent hyperinsulinemic hypoglycemia, due to defective nonneoplastic β-cells [2]. It is usually seen in newborns [130, 131] (a.k.a congenital hyperinsulinism [125, 126]); however, rare cases of adult nesidioblastosis do occur [96, 127–131].

Nesidioblastosis can be diagnosed biochemically, usually within the first few weeks of life, through a series of highly specialized tests of glucose, insulin, C-peptide levels, ketones, and glucagon response coupled with arterial calcium stimulation or percutaneous transhepatic pancreatic venous sampling [132]. However, heterogeneous clinical manifestation causes risk of late diagnosis or even misdiagnosis, which can lead to serious and permanent damage to the central nervous system and eventually, mental retardation [133].

Currently, there are three histological forms of nesidioblastosis: Focal, diffuse and atypical. Focal nesidioblastosis occurs when the abnormal islets are localized to a specific location in the pancreas. Diffuse form occurs when all the islets in the pancreas are abnormal. If a case is difficult to histologically categorize, it is regarded as atypical form [126, 134].

Alterations vary from patient to patient and may include

- relatively large collections of islet cells displacing acinar tissue,
- neoproliferation of islet cells from ducts (ductuloinsular complexes),
- islet cell “dysplasia” or nesidiodysplasia (loss of the usual centrilobular concentration of larger islets, increased numbers of small aggregates of islet cells distributed irregularly in the lobules, irregularity of the contour of the islets) or
- scattered islet cells (mostly β-cells cells) with enlarged and hypertrophic nuclei [130, 135–138].

However, none of these changes are specific for nesidioblastosis and would be confirmatory only in the right clinical context. Also, it should be kept in mind that in adults, hyperinsulinemic hypoglycemia is usually the result of a neuroendocrine neoplasm releasing insulin. Therefore, before nesidioblastosis diagnosis can be rendered, a diligent search for a neuroendocrine tumor is essential. In fact, the patient ought to be considered to have a neuroendocrine tumor unless definitively proven otherwise by systemic examination of the resected pancreas.

At a molecular level, genetic abnormalities in nine different genes [ATP binding cassette subfamily C member 8 *(ABCC8),* potassium channel, inwardly rectifying subfamily J, member 11 (*KCNJ11*), glutamate dehydrogenase 1 (*GLUD1*), glucokinase (*GCK*), hepatocyte nuclear factor 4 homeobox A (*HNF4A*), *HNF1A*, *SLC16A1* (also known as a monocarboxylate transporter, MCT1), uncoupling protein 2 (*UCP2*) and hydroxyacyl-CoA dehydrogenase *(HADH*)] have been identified in approximately half of the cases, indicating that there are as yet unidentified mechanisms involved in the regulation of insulin secretion [133].

Genetic abnormalities are classified into two categories namely: 'channelopathies' and 'metabolopathies' [139]. The former is attributed to the ATP-sensitive potassium channels (K_{ATP}) channel genes (*ABCC8* and *KCNJ11*) and latter to genes regulating different metabolic pathways (*GLUD1, GCK, HNF4A, HNF1A, SLC16A1, UCP2* and *HADH*). The most common disorders are those affecting the K_{ATP} channel genes and these are predominantly autosomal recessive. The other seven are less common but are autosomal dominant [133, 140, 141]. In most cases, diffuse form is inherited in an autosomal recessive manner, whereas focal form is sporadic [142, 143]. Patients with a homozygous recessive or a compound heterozygote mutation in their *ABCC8* or *KCNJ11* genes are usually medically unresponsive [140].

Partial to near-total pancreatectomy is the treatment of choice in cases refractory to aggressive medical management, although enucleation may be of value in controlling the symptoms in cases with focal nesidioblastosis. Diabetes mellitus and pancreatic insufficiency (malabsorption) may develop after pancreatectomy [127, 144–146].

Nesidioblastosis Key Features Box

Clinical

- Functional disorder of the β-cells
- Associated with persistent hyperinsulinemic hypoglycemia

Microscopic

- Can be focal or diffuse
- Pathologic findings vary greatly patient to patient
- Enlarged islets, abnormally shaped islets, ductuloinsular complexes and enlarged (a three-fold increase relative to the nuclei of adjacent islet cells) and hyperchromatic β-cell nuclei are common
- However, none of these changes are specific and would be confirmatory only in the right clinical context
- An insulinoma must be excluded by pathological examination before nesidioblastosis diagnosis can be rendered

Molecular

- Genetic abnormalities in nine different genes (*ABCC8, KCNJ11, GLUD1, GCK, HNF4A, HNF1A, SLC16A1, UCP2 and HADH*) have been identified in approximately half of the cases

LIPOMATOUS PSEUDOHYPERTROPHY

Focal replacement of the exocrine pancreas with mature adipose tissue is common in the pancreas and usually correlates directly with body mass index [147–149]. In contrast, lipomatous pseudohypertrophy is a distinct entity characterized by pseudotumor formation by adipose tissue, replacing almost an entire segment of exocrine parenchyma [150].

Most common symptom at presentation is abdominal pain [150]. In some cases, lipomatous pseudohypertrophy seems to be associated with specific syndromes such as Shwachman-Diamond or Johanson-Blizzard [151, 152] syndromes. Because it forms a mass, it is often mistaken for a malignancy [153]. On the other hand, if proper radiological evaluation is performed, it can be recognized that the lesion is actually composed of fat. Fine needle aspiration biopsy showing mature fat cells, without any atypia, might be helpful in such cases [154].

Approximately in 70% of the cases, there is a diffuse involvement of the pancreas; in 30%, the tumor is located in the head, body or tail only [150]. Macroscopically, the appearance and consistency are those of adipose tissue. Histological examination shows massive replacement of pancreatic parenchyma by mature adipose tissue. Although it does not appear to have a well-formed capsule, it has well-defined borders (Figure 15). The islets of Langerhans are relatively preserved, and typically there are scattered, small but well-preserved acinar elements. There is no significant inflammation. Adjacent pancreatic or soft tissue may show signs of compression.

At the microscopic level, the main differential diagnosis is with a well-differentiated liposarcoma, which is reported in the literature as individual case reports [66, 155]. The findings that speak against this possibility are the perfect maturation of lipocytes, sharp demarcation of the lesion, lack of lipoblasts, and admixture of normal pancreatic parenchyma within the lesion [150].

Lipomatous Pseudohypertrophy Key Features Box

Clinical

- May be mistaken for a malignancy

Microscopic

- Can be focal or diffuse
- Characterized by mature adipose tissue replacing the pancreatic parenchyma, leaving only scattered clusters of pancreatic elements
- Lipocytes are entirely normal, no lipoblast present

PARADUODENAL (GROOVE) PANCREATITIS

Paraduodenal pancreatitis (a.k.a. groove pancreatitis or cystic dystrophy of heterotopic pancreas) is a distinctive form of pancreatitis that occurs in the tissue between the duodenal wall and the pancreatic head. It often surrounds the minor ampulla and accessory duct [156–158].

The vast majority of patients are young males with a history of alcohol abuse. The most common symptom is severe waxing and waning upper abdominal pain. Frequent clinical findings include stenosis of duodenum, disordered gastric emptying, and postparandial vomiting. Weight loss is also a common finding and can be severe in some cases,

complicating the differential diagnosis with pancreas cancer [159–161]. ocal thickening and abnormal enhancement of the second portion of the duodenum and “tubulocystic” change in the vicinity of the accessory duct are specific features of this entity [162–164]. Those that have predominantly solid lesions, often related to the sclerotic changes in the periampullary region, are commonly diagnosed as “pancreas cancer” or “ampullary/periampullary neoplasm” [158, 162].

The reasons for this process to develop are not known. However, the macroscopic and microscopic findings are quite distinctive: The process leads to narrowing of the duodenal lumen and the duodenal mucosa often acquires a nodular or cobblestone appearance [165]. Upon sectioning, the duodenal wall shows a trabeculated appearance, often accompanied by cystic change, especially in the vicinity of the minor ampulla. In some cases, cyst formation may be prominent, measuring up to several centimeters in size, mimicking intestinal duplication.

Microscopically, the duodenal mucosa often reveals Brunner’s gland hyperplasia and there is an exuberant myofibroblastic proliferation, often arranged in fascicles (Figure 16) accompanied by small, well-circumscribed lobules of pancreatic tissue (“myoadenomatosis” pattern) or variably sized ducts (“cystic dystrophy of heterotopic pancreas”). These ducts may contain inspissated acinar enzymes. The cyst contents may extravasate and lead to the development of a foreign-body giant cell reaction and stromal eosinophilia. Some cysts are devoid of epithelium (Figure 17). Instead, they are lined by more cellular fibroblastic tissue [158, 164]. Prominence of nerve bundles mimicking traumatic neuroma is also common.

It should be kept in mind that, as in any case of pancreatic pathology, before the diagnosis of paraduodenal pancreatitis is rendered, the possibility of adenocarcinoma ought to be carefully excluded, since it can mimic any form of pancreatitis, and be associated with any of the changes characteristic of this lesion.

Paraduodenal Pancreatitis Key Features Box

Clinical

- Predominantly in 40 to 50 years old males
- History of alcohol abuse is common
- Patients present with waxing and waning severe upper abdominal pain and postparandial vomiting
- Predominantly solid ones radiographically mimic pancreatic or ampullary/periampullary tumors

Macroscopic

- Often centered in the region of minor papilla
- Trabeculation of duodenal musculature with occasional cysts is common
- Paraduodenal wall cyst (measuring up to 10 cm) mimicking intestinal duplication may occur

Microscopic

- Dense myoid stromal proliferation with intervening rounded lobules of pancreatic tissue (“myoadenomatosis’)
- Brunner’s gland hyperplasia
- Extravasated (stromal) mucoprotein plugs surrounded by eosinophiles or multinucleated giant cells

CONCLUSIONS

Benign neoplasms and tumor-like (pseudotumoral) lesions of the pancreas can be challenging, mostly due to lack of familiarity because of the lower number of cases, compared to malignant neoplasms, pathologists encounter on a daily basis.

Well-demarcated and sponge-like appearance with innumerable small cysts of *microcystic* serous cystadenomas is so characteristic and usually does not create any diagnostic problems. In contrasts, macrocytic serous cystadenomas can be difficult to diagnose as the lining epithelium might be extremely attenuated. Inflammatory myofibroblastic tumors may have overlapping morphologic features with IgG4-related autoimmune pancreatitis (discussed separately in this issue). However, it is different from autoimmune pancreatitis in terms of the ALK expression, low-level of IgG4+ cell infiltration and lack of obstructive phlebitis.

A variety of non-neoplastic conditions may also form a cystic or solid mass mimicking a malignant neoplasm in the pancreas. Up to 5% of pancreatectomies performed with the preoperative clinical diagnosis of malignant neoplasm will prove to be non-neoplastic by pathologic examination, although this figure is decreasing with improved diagnostic modalities. Lymphoepithelial cyst, epidermoid cyst in intrapancreatic accessory spleen and squamoid cyst of pancreatic ducts are all cystic lesions lined by usually squamous epithelium and recognition of the accompanying elements (lymphoid tissue with or without germinal centers, splenic tissue, etc) is necessary for a correct diagnosis. Heterotopic pancreas may form a well-defined nodule within the duodenum and is typically mistaken for neuroendocrine neoplasm. Hamartomas are very rare if the entity is defined strictly. They are characterized by irregularly arranged mature pancreatic elements admixed with stromal tissue. None of the pathologic findings of nesidioblastosis such as enlarged islets, abnormally shaped islets, ductuloinsular complexes and enlarged/hyperchromatic β-cell nuclei are specific and would be confirmatory only in the right clinical context. Lipomatous hypertrophy is the replacement of pancreatic tissue with mature adipose tissue that occasionally leads to moderate to marked enlargement of the pancreas. Chronic inflammatory lesions are the leading cause of “pseudotumoral pancreatitis”, and among these, autoimmune and paraduodenal pancreatitides are most important.

In conclusion, it is important to recognize all these benign neoplasms and types of conditions that form pseudotumors in the pancreas so that they can be distinguished from malignant neoplasms, especially ductal adenocarcinomas.

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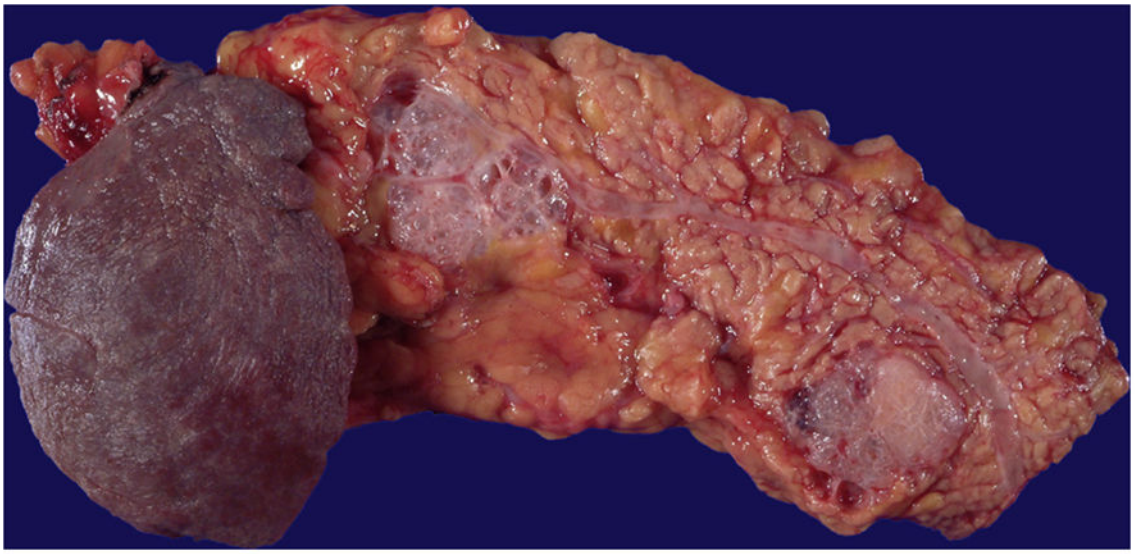

Figure 1.

Two *microcystic* serous cystadenomas are present in this distal pancreas. The neoplasms are well-demarcated and composed of numerous small cysts, the majority of which measure in submillimeters.

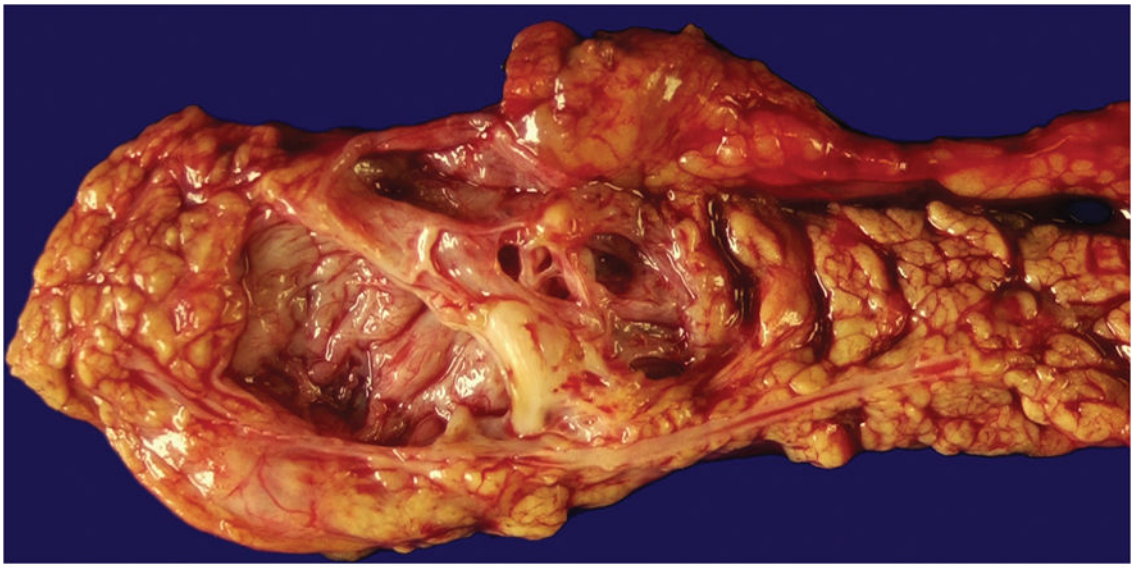

Figure 2.

Macrocystic (oligocystic) serous cystadenoma has either a singular locule or a few locules (as illustrated here) with a flattened lining.

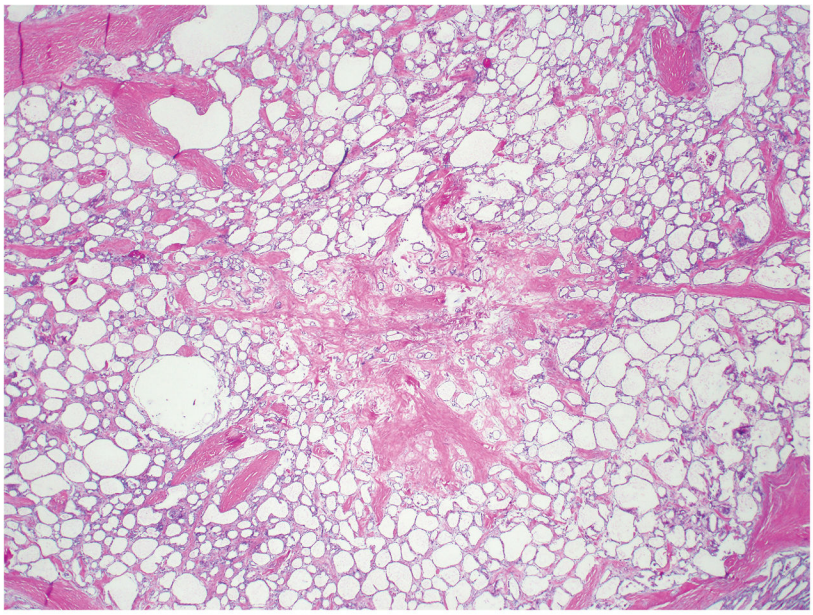

Figure 3.

Microcystic serous cystadenoma is characterized by numerous small, irregular tubular structures of variable shapes. Note the hyalinized stroma at the centre.

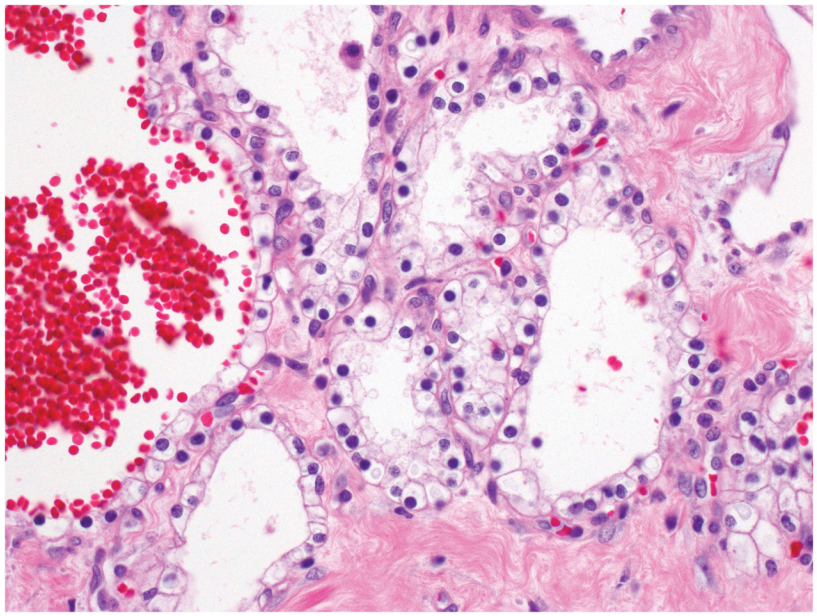

Figure 4.
The cysts of serous cystadenomas are lined by cuboidal cells, with round, central to slightly eccentric nuclei and clear cytoplasm.

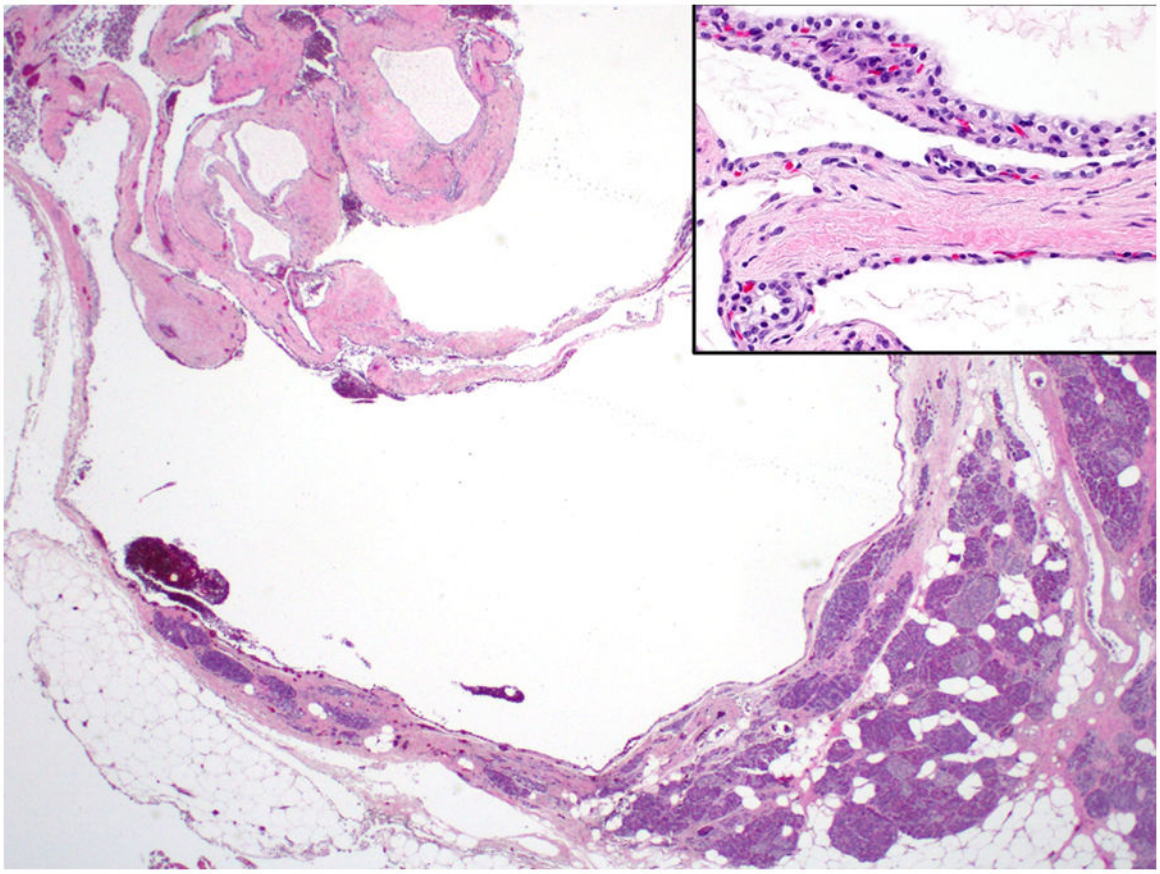

Figure 5.

Although the cysts are fewer and larger than in the *microcystic* serous cystadenoma, *macrocystic (oligocystic)* serous cystadenoma is also lined by the same cuboidal cells with clear cytoplasm (inset).

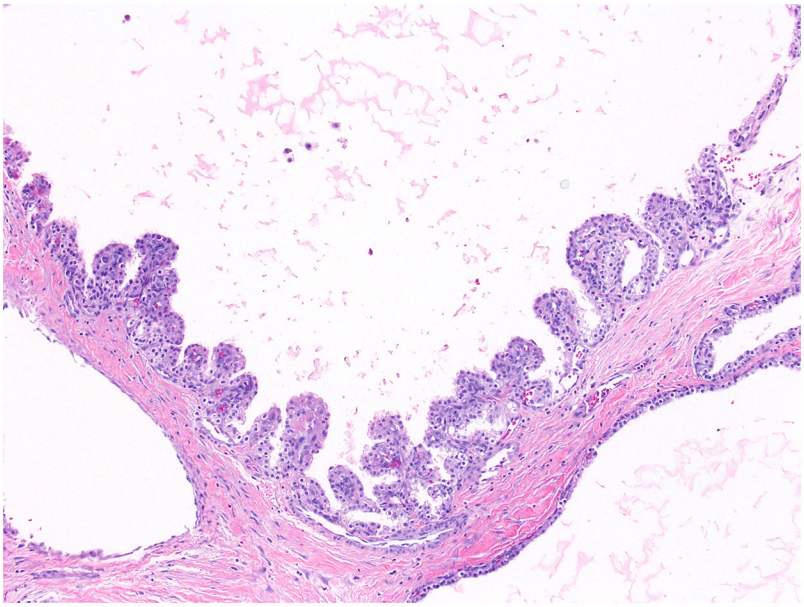

Figure 6.
Although the lining epithelium is usually flat, prominent but stubby papillary projections might be seen in some serous cystadenomas.

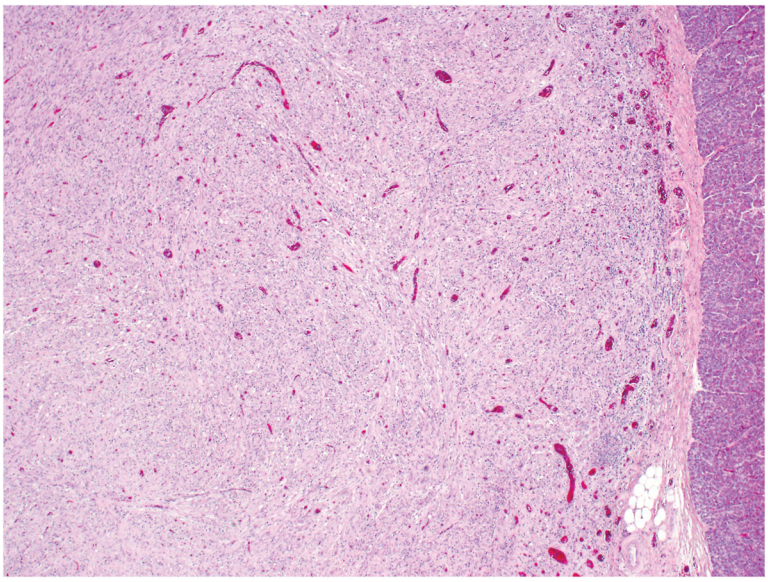

Figure 7.
Inflammatory myofibroblastic tumor with well-defined margins.

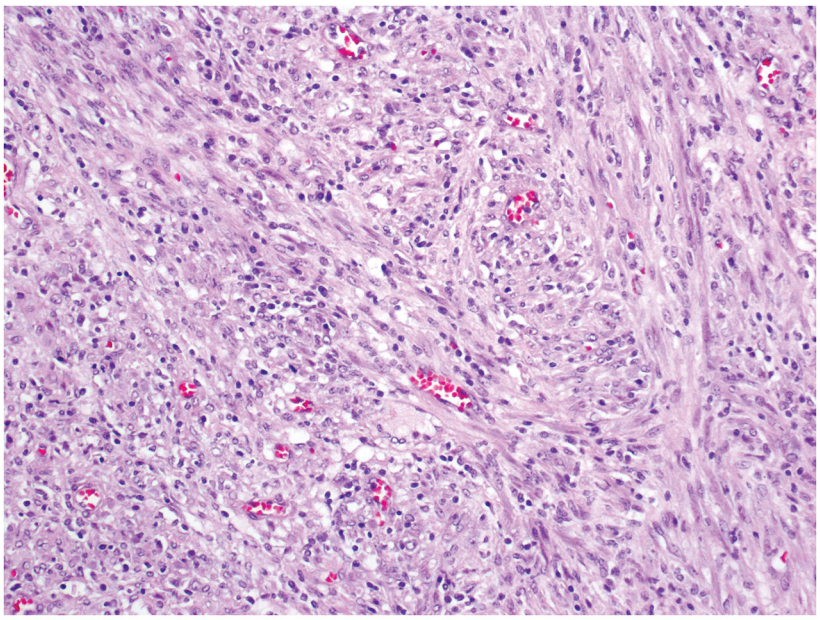

Figure 8.

Proliferation of generally bland spindle mesenchymal cells arranged in irregular fascicles into a stroma with lymphocytes, plasma cells, and histiocytes is characteristic in inflammatory myofibroblastic tumor.

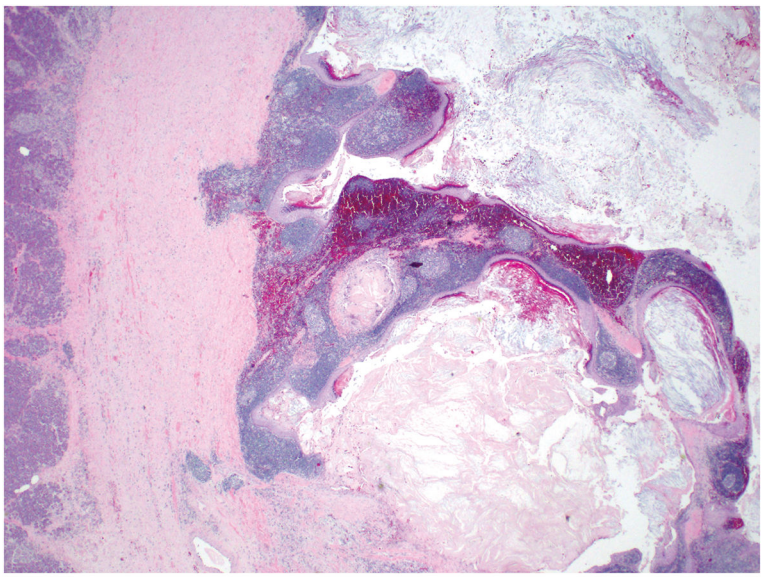

Figure 9.

A lymphoepithelial cyst lined by mature, stratified squamous epithelium with keratinization. Note the lymphoid tissue with germinal center formation immediately beneath the epithelium.

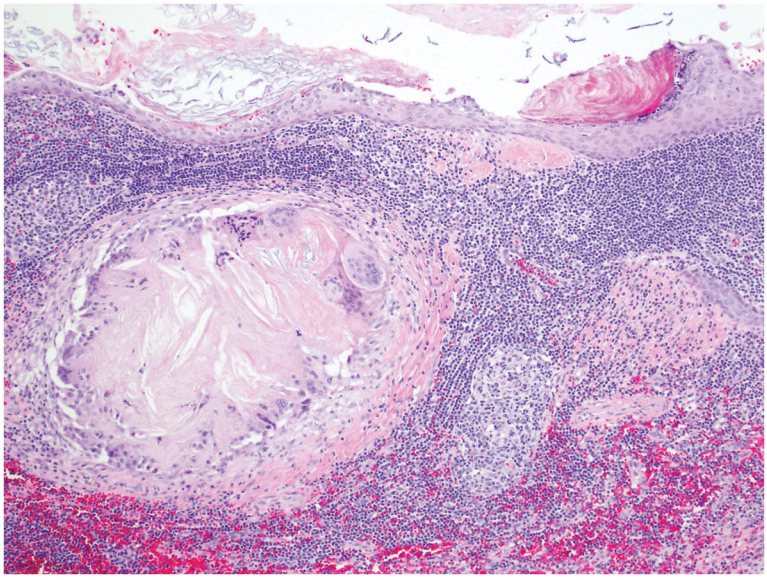

Figure 10.
Epithelioid granulomas and cholesterol clefts may also be present beneath the lining epithelium of lymphoepithelial cysts.

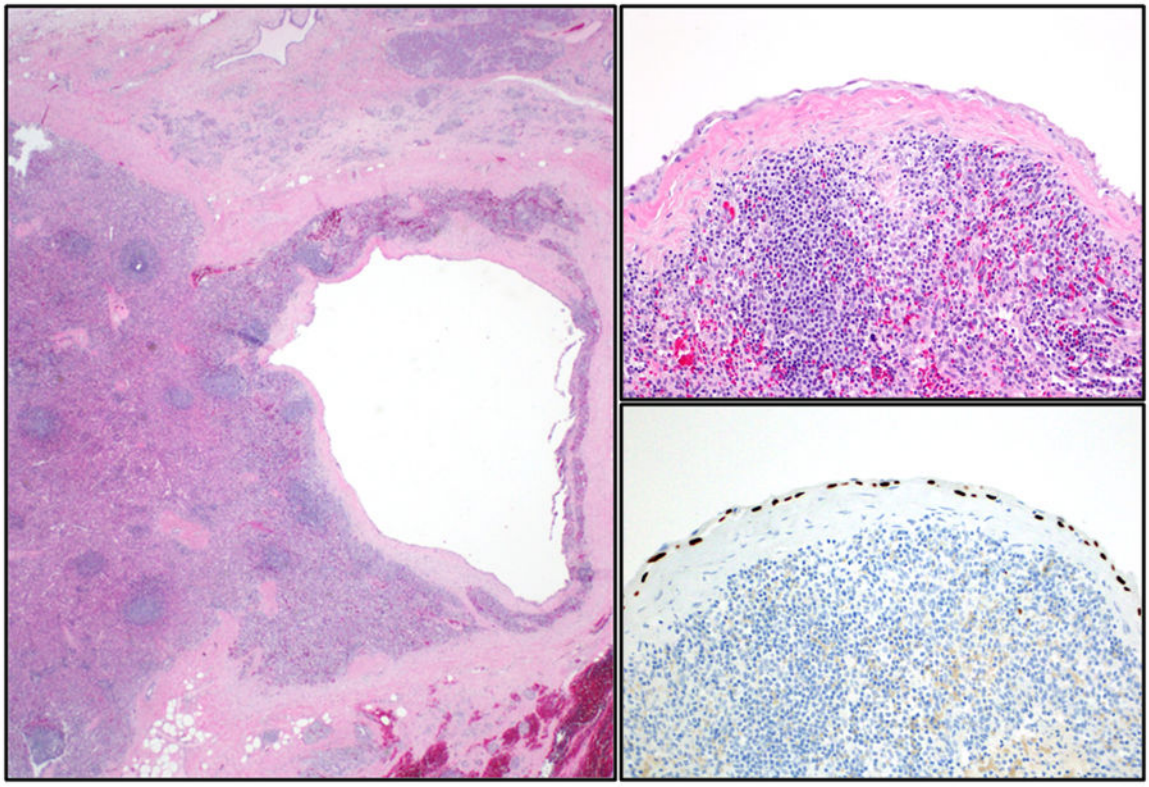

Figure 11.

Epidermoid cyst in intrapancreatic heterotopic spleen has a thin lining surrounded by splenic red and white pulp (left). Recognition of the splenic elements allows a correct diagnosis even if the squamous nature of the attenuated lining epithelium (top right) may not be appreciated without immunohistochemical staining (bottom right, p63 immunohistochemical stain).

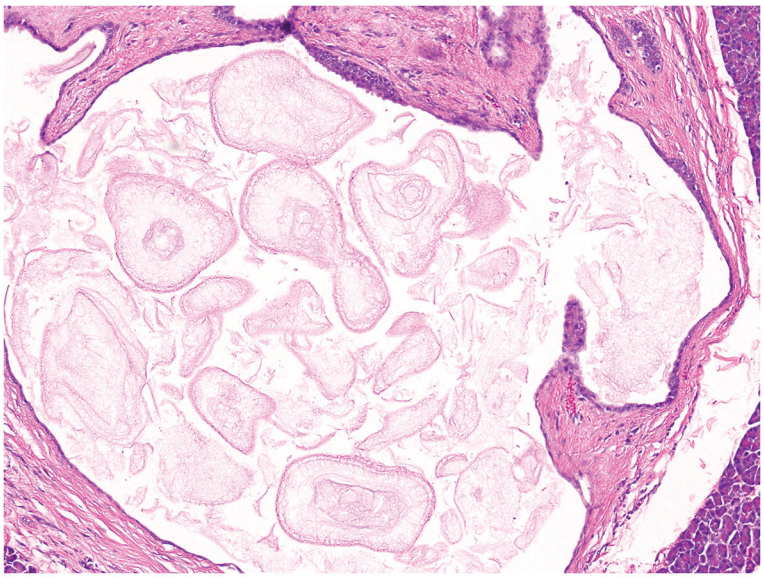

Figure 12.
Squamoid cyst of pancreatic duct showing unilocular and well-circumscribed cyst filled with dense mucoproteinaceous material, characteristic of enzymatic concretions.

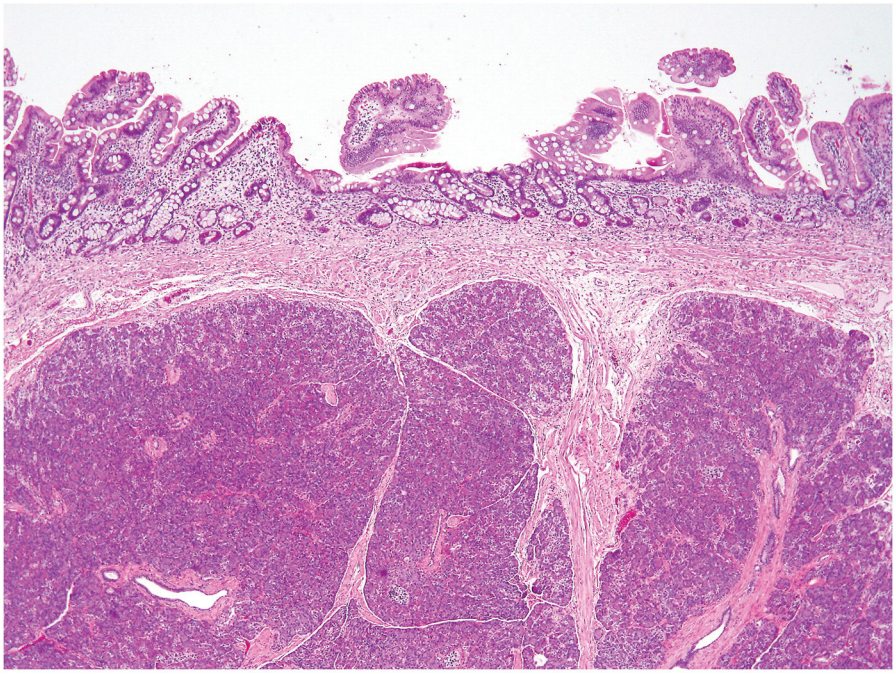

Figure 13.
Heterotopic pancreas, containing all of the normal pancreatic elements, in the duodenal submucosa.

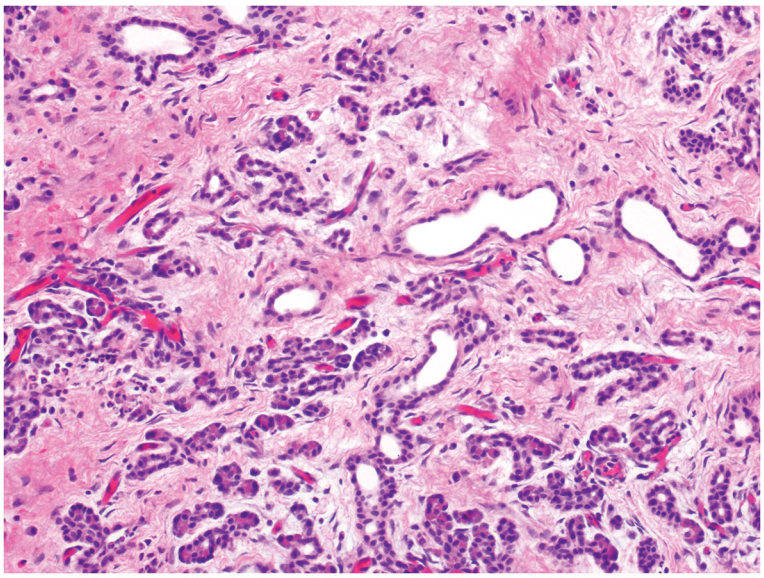

Figure 14.
Pancreatic hamartoma with cystic ductal structures and disorganized acini embedded in a fibroblastic stroma. Note that islets are not present.

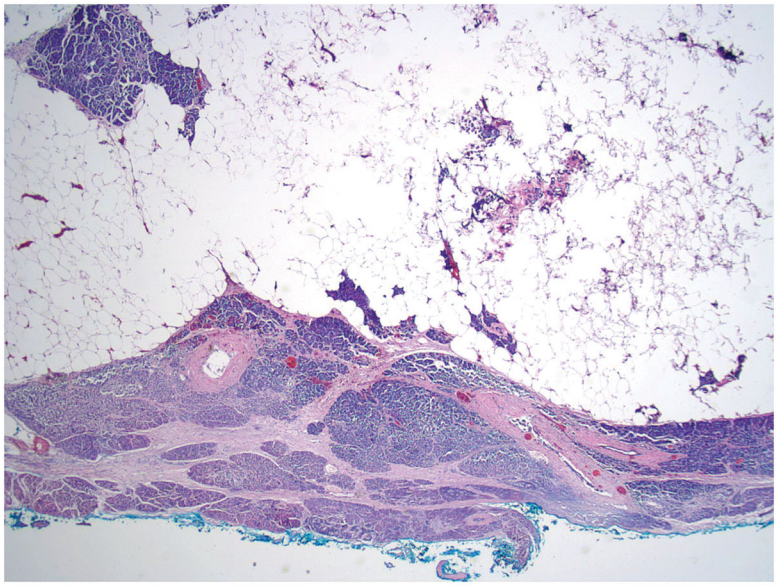

Figure 15.

Well-circumscribed lipomatous pseudohypertrophy, composed of mature adipose tissue, pushing into the adjacent pancreas is illustrated. Scattered acini within the adipose tissue are also visible.

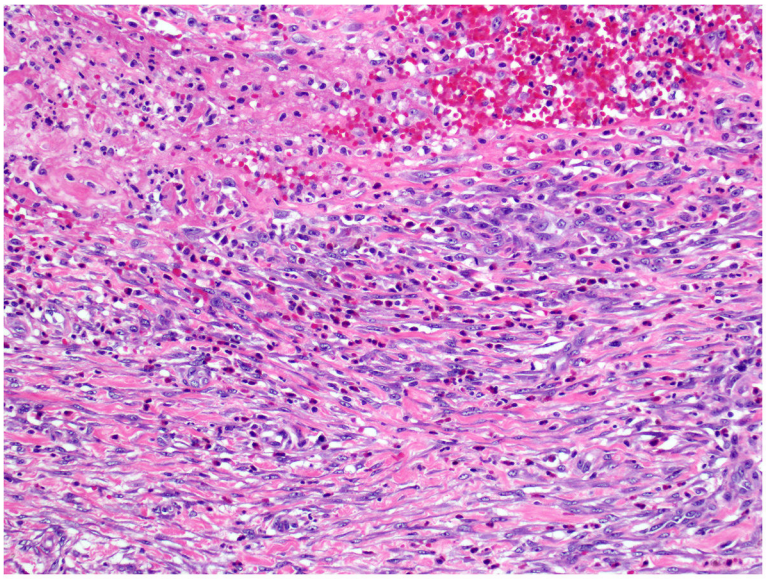

Figure 16.
In paraduodenal (groove) pancreatitis, there is a striking reactive spindle cell proliferation, including, smooth muscle cells and myofibroblasts, associated with inflammatory cells.

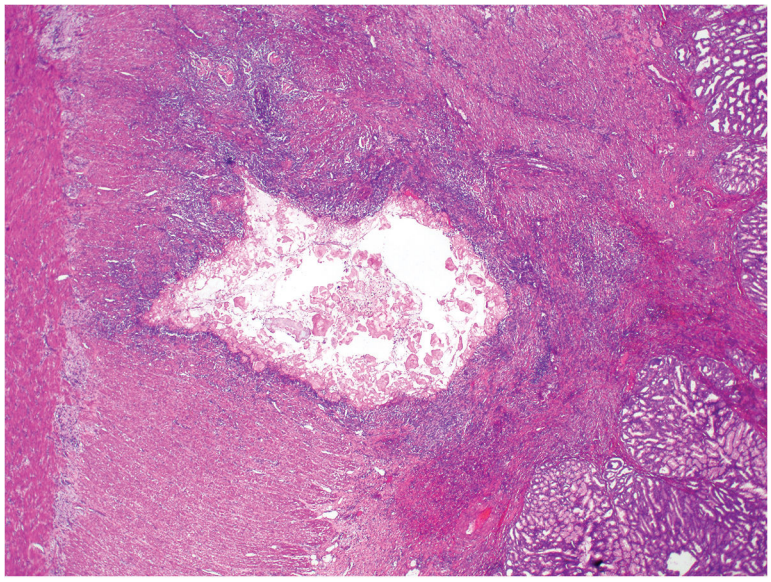

Figure 17.

Characteristically, the cysts of paraduodenal (groove) pancreatitis contain eosinophilic, amorphous inspissated enzymatic secretions and are surrounded by markedly inflamed fibrous tissue. Note the abundant Brunner's glands on the right.