Serous Cystic Neoplasia

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Serous cystic neoplasms are composed of uniform cuboidal, glycogen-rich, epithelial cells lining cysts of varying sizes. These cysts contain watery serous fluid. In clinical practice, serous cystic neoplasms are considered entirely benign. There are, however, very rare examples of serous cystadenocarcinoma in the literature, but some question whether they represent multifocal disease rather than metastatic malignant neoplasm.

15.1 WHO Classification

Serous cystic neoplasms are included in 'benign epithelial tumors and precursors' in the 2019 WHO classification of tumors of the pancreas [1].

15.2 Terminology

Serous cystadenoma is also known as glycogen-rich cystadenoma, serous microcystic adenoma, or microcystic serous adenoma. The macrocystic variant is known as macrocystic serous cystadenoma, oligocystic serous cystadenoma, or serous oligocystic and ill-demarcated adenoma.

In this chapter, we will use the terms '*microcystic serous cystadenoma*' and '*macrocystic serous cystadenoma*' for the two commonest variants.

15.3 Epidemiology

Serous cystic neoplasms are uncommon, accounting for 1–2% of exocrine pancreatic neoplasms and for 10% of resected cystic pancreatic lesions. Microcystic serous cystadenoma is the most common variant. The mean age at presentation for microcystic serous cystadenoma is 60 years and for macrocystic serous cystadenoma is 50 years (range 18–93 years). The macrocystic variant has also been described in infants under 18 months of age. Serous cystic neoplasms are more common in females.

15.4 Clinical Features

The majority of patients with a serous cystic neoplasm are asymptomatic and the tumor is detected on imaging or at laparotomy. Symptoms include abdominal pain, nausea and vomiting, weight loss, or a palpable mass, and are usually related to location of the tumor in the head of the pancreas [2]. Serous cystic neoplasms may occasionally compress or obstruct the pancreatic duct or the common bile duct. However, jaundice is extremely unusual. Serum tumor markers are generally not raised.

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15.4.1 Associations

The etiology is unknown. A small minority of serous cystadenomas may be associated with von Hippel-Lindau (VHL) syndrome (see Chap. 20, Sect. 20.12). There are rare cases of serous cystic neoplasms co-existing with other neoplasms including pancreatic ductal adenocarcinoma and ampullary adenocarcinoma. Serous cystic neoplasms may also co-exist with grade 1–3 pancreatic neuroendocrine tumors (PanNETs); von Hippel-Lindau syndrome should always be considered when this occurs.

15.4.2 Imaging

On CT scan or endoscopic ultrasound scan, microcystic serous cystadenoma appears as a well-circumscribed mass composed of tiny (less than 1–2 cm in size) cysts separated by fine septa with a characteristic central stellate fibrous scar. In approximately a third of cases, there is a 'sunburst' pattern of calcification in the central scar.

Macrocystic serous cystadenoma is composed of larger cysts (1–3 cm in size, or larger) and may even be unilocular. On imaging, they are poorly circumscribed, do not have a central scar, and may mimic a mucinous cystic neoplasm (see Chap. 16) or a branch-duct-type intraductal papillary mucinous neoplasm (see Chap. 17).

Serous cystic neoplasms do not usually communicate with the pancreatic duct system. However, there are rare case reports in which microcystic and macrocystic serous cystadenomas have been found to communicate with the duct system [3].

The solid variant of serous cystic neoplasms (see Sect. 15.11.1) may be mistaken for a neuroendocrine tumor on imaging.

The newly emerging technique endoscopic ultrasound-guided needle-based confocal laser endomicroscopy can be used to identify serous cystic neoplasms on preoperative evaluation of pancreatic cysts, by visualizing the capillary plexus beneath the epithelial lining, which is characteristic of serous cystic neoplasms [4].

15.5 Classification

There are six types of serous cystic neoplasm:

1. Microcystic serous cystadenoma,
2. Macrocystic serous cystadenoma,
3. Solid serous adenoma,
4. von Hippel-Lindau syndrome-associated serous cystic neoplasm,
5. Mixed serous-neuroendocrine neoplasm, and
6. Serous cystadenocarcinoma.

15.6 Macroscopy

15.6.1 Microcystic Serous Cystadenoma

Microcystic serous cystadenomas may occur anywhere within the pancreas, but the majority arise in the body and tail of the pancreas. They are usually solitary, well-circumscribed, bosselated, round tumors with an incomplete fibrous pseudocapsule or, more commonly, no capsule at all. The adjacent pancreas is usually macroscopically normal. Multiple serous cystic neoplasms should always raise the possibility of von Hippel-Lindau syndrome. The mean size is 4–5 cm (range 1–30 cm) and they may compress or displace the main pancreatic duct or common bile duct (Fig. 15.1).

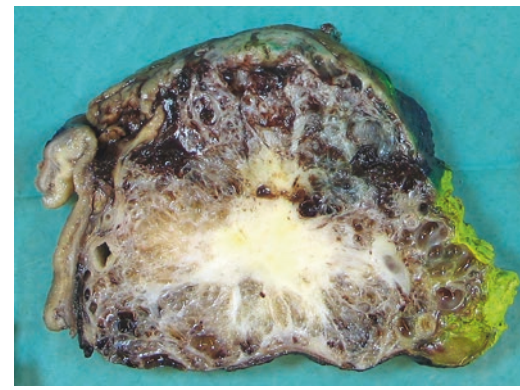

Fig. 15.1 Microcystic serous cystadenoma: there is a large central scar with radiating fibrous septa and small cysts. The neoplasm compresses the bile duct (*left* of picture)

The cut-surface is sponge-like (also referred to as honeycomb-like) with numerous tiny, thin-walled cysts (usually less than 2–10 mm in size) filled with clear watery fluid (Fig. 15.2). There is a central fibrous scar, which may be calcified, with fibrous septa radiating out towards the periphery (Figs. 15.1 and 15.2). The adjacent pancreas may be entirely normal or show obstructive changes, including chronic pancreatitis and fatty replacement (Figs. 15.2 and 15.3). There may be irregular extension of the neoplasm into the adjacent pancreas, duodenum (Fig. 15.4), peripancreatic lymph nodes, or large blood vessels, sometimes referred to as 'locally aggressive behavior' (see Sect. 15.11.6).

Fig. 15.2 Microcystic serous cystadenoma: there is a honeycomb or sponge-like cut-surface and central radiating scar. Note the surrounding pancreas is entirely normal

15.6.2 Macrocystic Serous Cystadenoma

Macrocystic serous cystadenomas occur most commonly in the head of the pancreas. They are usually solitary and may be well circumscribed but, more commonly, are ill-demarcated and extend into the adjacent pancreas. The mean size is 4 cm (range 2–15 cm).

The cut-surface reveals a few thin-walled cysts ranging in size from 1 to 8 cm and filled with

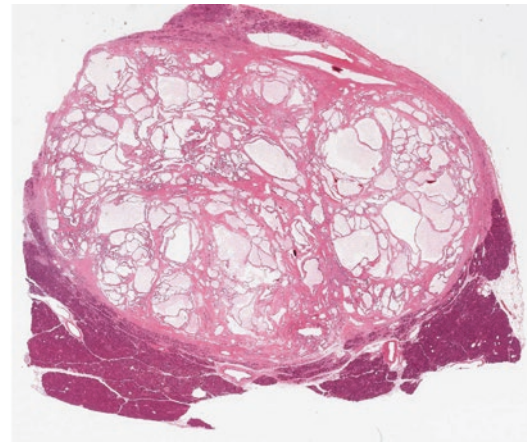

Fig. 15.3 Microcystic serous cystadenoma: this whole-mount cross-section shows a well-circumscribed neoplasm that is associated with fibrosis and atrophy of only the peritumoral pancreatic parenchyma

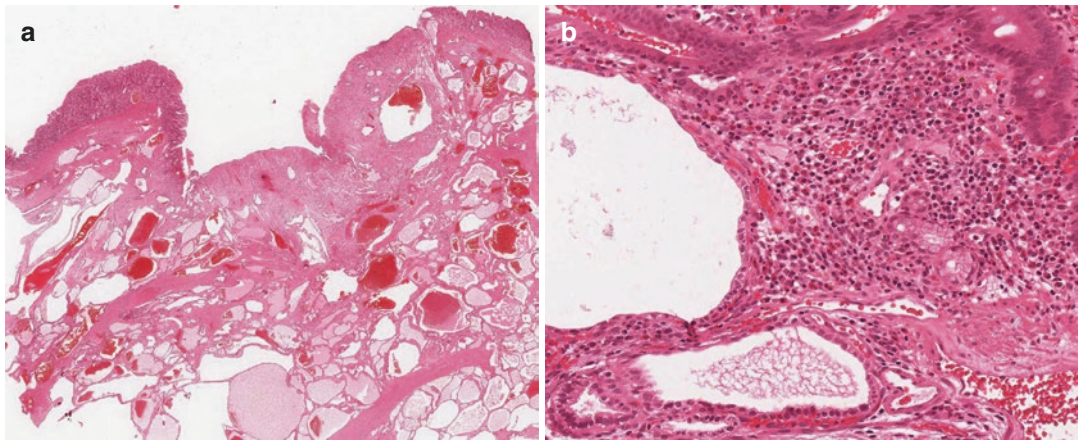

Fig. 15.4 Microcystic serous cystadenoma: this whole-mount cross-section shows extension of the neoplasm into the ulcerated duodenum with associated hemorrhage in the neoplasm (**a**). At higher power, the neoplastic cysts (*left*) are seen within the duodenal mucosa next to duodenal glands and Brunner's glands (**b**)

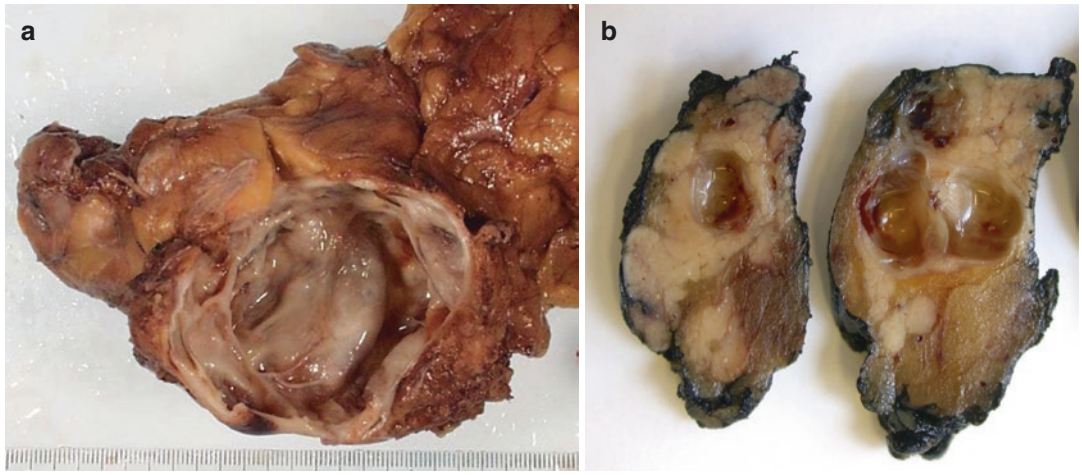

Fig. 15.5 Macrocystic serous cystadenoma: the wall is thin and there is a smooth lining (**a**). This smaller example contains watery fluid and is surrounded by normal pancreas (**b**)

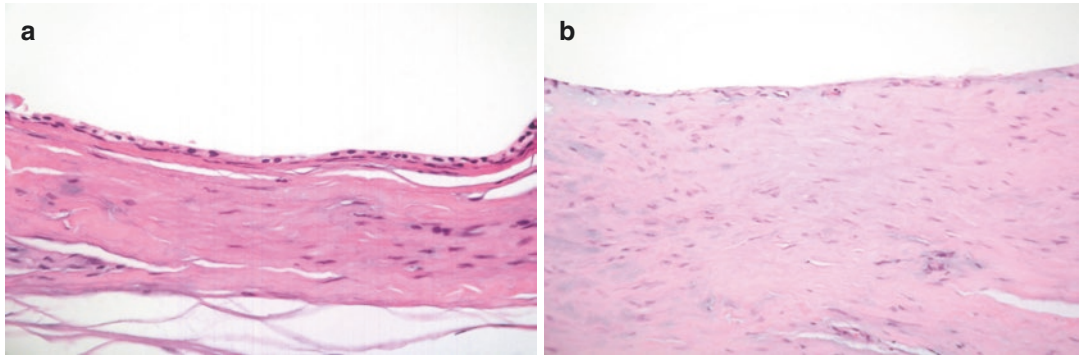

Fig. 15.6 Macrocystic serous cystadenoma: this unilocular cyst only showed focal epithelial lining (**a**). Most of the epithelium was denuded, mimicking a pseudocyst (**b**)

clear watery fluid (Fig. 15.5). Some examples may be unilocular. The inner lining of the cysts is smooth and there is no central stellate scar.

15.6.3 Sampling

Microcystic serous neoplasms do not need extensive sampling. However, much of the epithelium in macrocystic serous cystadenomas can be denuded (Fig. 15.6 and see Chap. 14, Sect. 14.2) and, therefore, these should be sampled extensively to confirm the diagnosis and/or distinguish them from other oligocystic pancreatic lesions.

15.7 Microscopy

The cysts in microcystic serous cystadenoma and macrocystic serous cystadenoma are lined by a single layer of uniform, cuboidal, epithelial cells with clear cytoplasm (due to abundant glycogen) and central round/oval hyperchromatic nuclei with inconspicuous nucleoli (Fig. 15.7a). Occasionally, the cytoplasm may be eosinophilic and granular. The neoplastic cells may be flattened and attenuated with little visible cytoplasm or may form intracystic microscopic papillae (Fig. 15.8a), occasionally with fibrovascular cores (Fig. 15.8b). These papillae are of no clinical significance. There may be occa-

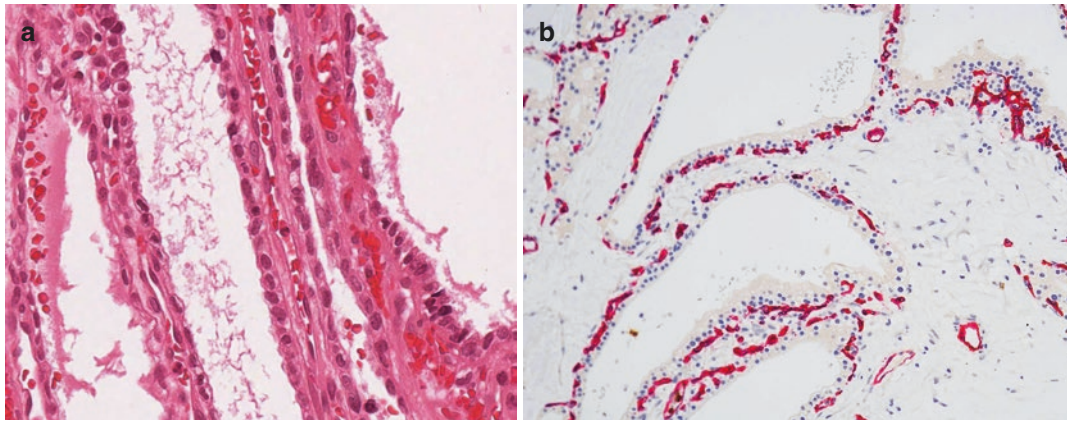

Fig. 15.7 Microcystic serous cystadenoma: the cysts are lined by cuboidal epithelial cells with clear cytoplasm and small, round, hyperchromatic nuclei (**a**). Prominent small capillary-sized vessels are present beneath the epithelium, which are highlighted on CD34 immunohistochemistry (**b**)

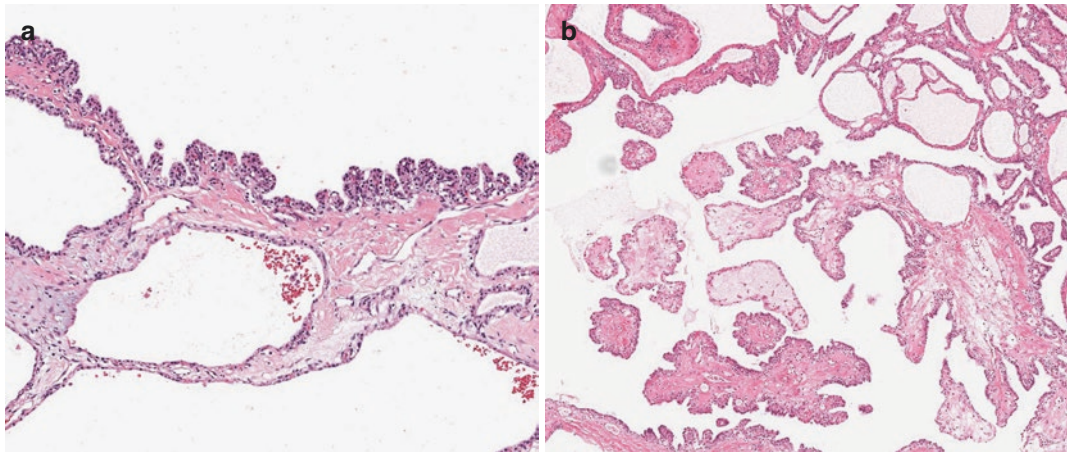

Fig. 15.8 Microcystic serous cystadenoma: there may be intracystic micropapillae (**a**) or larger papillae with fibrovascular cores (**b**). These are of no clinical significance

sional larger nuclei, but mitotic figures, nuclear pleomorphism, and necrosis are not found. There is a prominent network of small capillary-sized vessels immediately beneath the epithelium in microcystic serous cystadenoma (Fig. 15.7b) and macrocystic serous cystadenoma, which can be visualized in the latter, preoperatively, using endoscopic ultrasound-guided needle-based confocal laser endomicroscopy [4].

The central scar and radiating septa in microcystic serous cystadenoma are composed of hyalinized collagen, which can be calcified (Fig. 15.9), and may contain entrapped nerves, lymphocytic aggregates, acinar tissue, ducts, and islets (Fig. 15.10). Amyloid has also been described within the stroma [5]. There may be tiny cysts within the central scar and focal degenerative changes including cholesterol clefts, foreign-body-type giant cells, hemosiderin, inflammation, and calcification (Fig. 15.11).

Serous cystic neoplasms often show irregular extension into the adjacent pancreas, which may show atrophic changes.

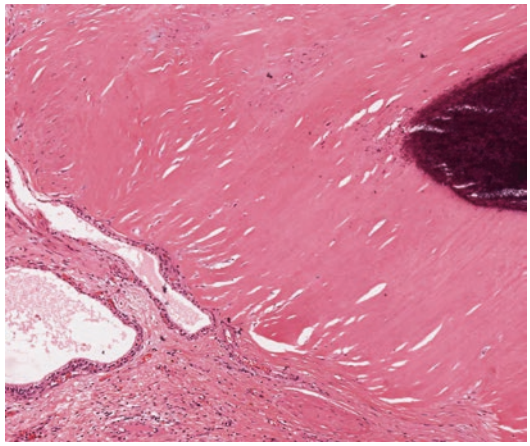

Fig. 15.9 Microcystic serous cystadenoma: the central scar is composed of sclerotic collagen which may be calcified, as seen here (*right* of picture)

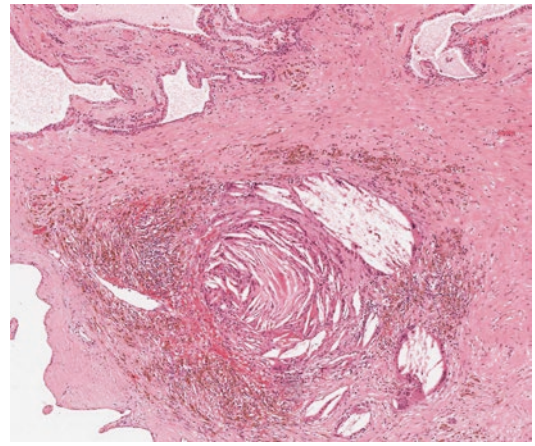

Fig. 15.11 Microcystic serous cystadenoma: there may be focal degeneration with hemosiderin-laden macrophages and foreign body-type giant cells surrounding cholesterol clefts

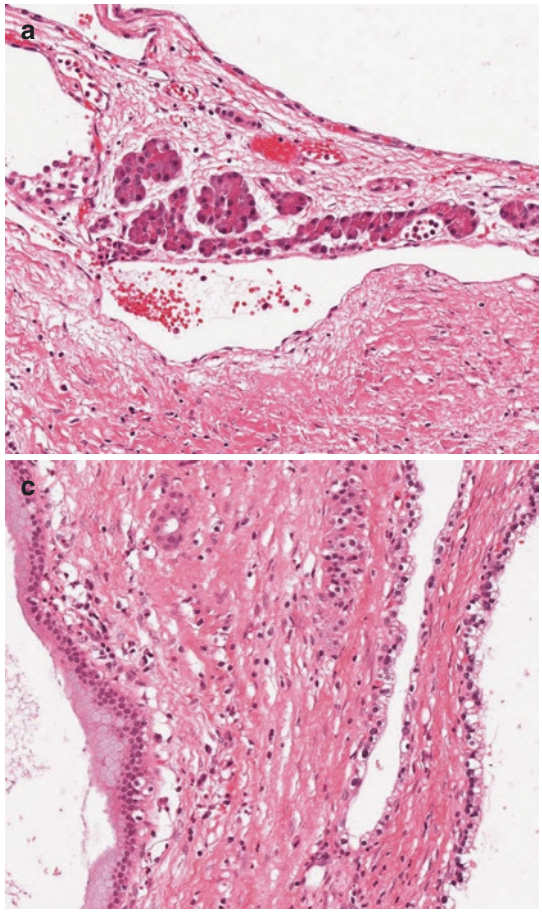

Fig. 15.10 Microcystic serous cystadenoma: there may be entrapped acini and islet cells (**a**) or ducts within the fibrous tissue. This entrapped duct shows low-grade PanIN (**b**). The tall mucinous epithelium of low-grade PanIN (*left* of picture) is readily distinguished from the clear cuboidal cells of the serous cystadenoma (**c**)

15.8 Histochemistry

Periodic acid Schiff (PAS) stains the abundant glycogen within the cytoplasm. Stains for mucin (PAS-diastase, mucicarmine, and alcian blue) are negative.

15.9 Immunohistochemistry

Serous cystic neoplasms express epithelial markers AE1-AE3, CAM5.2, EMA, CK7, CK8, CK18, and CK19. There may also be expression of MUC1, MUC6, alpha-inhibin, CAIX, and NSE. Beta-catenin immunohistochemistry shows normal membranous staining. Ki67 proliferative index is very low.

Serous cystic neoplasms are usually immunonegative for CEA, MUC2, MUC5AC, CK20, chromogranin A, synaptophysin, vimentin, and pancreatic hormones.

Immunohistochemistry is not usually needed to make the diagnosis of a serous cystic neoplasm, but may be helpful in diagnosing a macrocystic serous neoplasm when the epithelium is scanty and/or attenuated. Similarly, immunohistochemistry may be useful to confirm the diagnosis of a solid serous adenoma (see Sect. 15.11.1) and exclude other differential diagnoses, such as metastatic renal cell carcinoma (see Sect. 15.12).

15.10 Molecular Pathology

Loss of heterozygosity or (loss of function) mutations of the *VHL* tumor suppressor gene can be found in most sporadic serous neoplasms, and in all von Hippel-Lindau syndrome-associated serous neoplasms. These genomic alterations can be detected in pancreatic cyst fluid, which may aid preoperative diagnosis [6].

15.11 Rare Variants

15.11.1 Solid Serous Adenoma

This rare variant was first described in 1996 [7] and lacks the macroscopic cysts of the microcystic and macrocystic variants. The neoplasm is well-circumscribed, solid, pale, and typically small (2–4 cm in size). It may be admixed with a typical cystic serous neoplasm (Fig. 15.12). On microscopy, the neoplasm is composed of lobules of closely-packed clear epithelial cells, arranged in nests, sheets, and small acini with small central lumina, separated by collagenous stroma (Fig. 15.13). The cells are identical to those seen in serous cystadenomas. The delicate capillary network seen beneath the epithelium of the serous cystadenomas (see Sect. 15.7) is also present in solid serous adenoma (Figs. 15.13c, d). This combination of clear cells (arranged in nests or acini) and intervening vascular network can mimic a clear cell variant of pancreatic neuroendocrine tumor (see Sect. 15.12.3) or metastatic renal cell carcinoma (see Sect. 15.12.1).

15.11.2 von Hippel-Lindau Syndrome-Associated Serous Cystic Neoplasm

Serous cystic neoplasms are the most common pancreatic lesions found in patients with the rare autosomal dominant disorder von Hippel-Lindau (VHL) syndrome. These patients develop serous cystic neoplasms of the pancreas at a younger age (mean 32 years) than those patients with

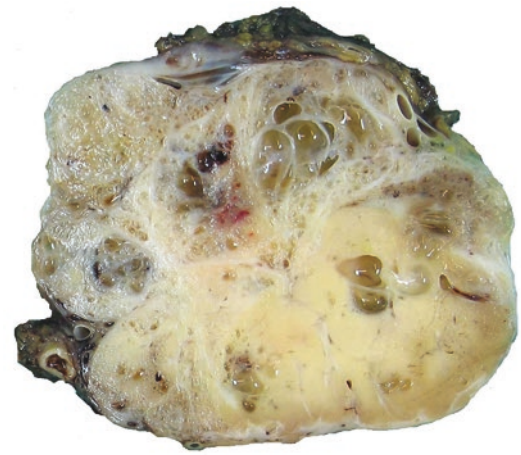

Fig. 15.12 Combined microcystic serous cystadenoma and solid serous adenoma: solid serous adenoma may be entirely solid, but in this example there was typical microcystic serous cystadenoma (*uppermost*) and solid serous adenoma in the same lesion

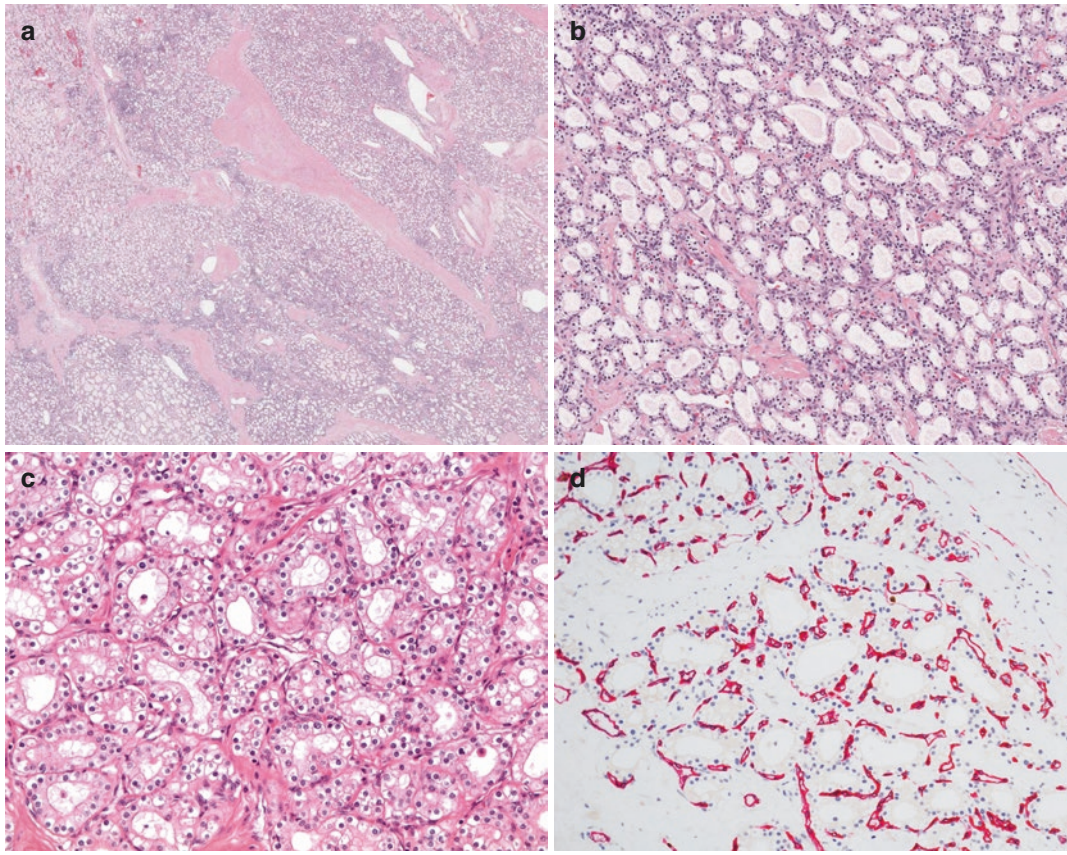

Fig. 15.13 Solid serous adenoma: there is a solid lobulated architecture with fibrous bands (**a**) between closely packed small acini of clear cuboidal cells, which are identical to those seen in serous cystadenomas (**b**). At higher power, small capillary-sized vessels can be seen between the acini of cuboidal cells (**c**), and are highlighted on CD34 immunohistochemistry (**d**)

nonsyndromic serous cystic neoplasms (mean age 50–60 years). The serous cystic neoplasms are usually multiple, macrocystic, and typically involve the whole pancreas diffusely (Fig. 15.14) or in a patchy fashion. VHL patients may also develop pancreatic endocrine neoplasms and mixed serous-neuroendocrine neoplasm of the pancreas, typically composed of a grade 1–3, clear cell, pancreatic neuroendocrine tumor (PanNET) with a serous cystadenoma (see Sect. 15.11.5).

Pancreatic cysts may be the first presentation of VHL syndrome and, therefore, when multiple pancreatic serous cystic neoplasms or a mixed serous-neuroendocrine neoplasm are diagnosed, the possibility of VHL syndrome should be raised.

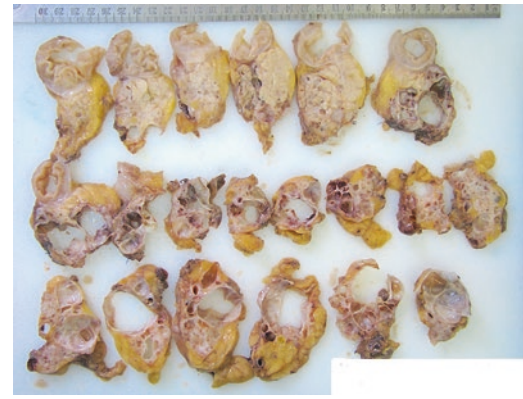

Fig. 15.14 von Hippel-Lindau syndrome: there is diffuse involvement of the pancreas by serous cystic neoplasia

15.11.3 Microcystic Serous Cystadenoma with Subtotal Cystic Degeneration

Microcystic serous cystadenoma with subtotal cystic degeneration has been described [8]. Extensive degeneration within a microcystic serous neoplasm may result in a unilocular or multilocular cystic lesion, which radiologically, macroscopically, and microscopically can mimic a pseudocyst. Multilocular cases retain focal macroscopic features of a microcystic serous cystadenoma, but these gross features are not present in the unilocular examples. The neoplasm has a well-defined border and the adjacent pancreas may be normal or show peritumoral fibrosis.

Microscopically, much of the epithelial lining is denuded and the cyst wall is fibrotic with associated chronic inflammation, foamy macrophages, cholesterol clefts, reactive myofibroblasts, hemorrhage, and hemosiderin, resembling the wall of a pseudocyst. Foci of residual epithelium are found embedded within the fibrotic wall, forming small solid nests or submillimeter-sized cysts, which are surrounded by a dense network of small capillary-sized vessels. The epithelium is identical to that seen in all serous cystic neoplasms, but may be attenuated with minimal cytoplasm.

This entity differs from a macrocystic serous cystadenoma, which is composed of thin-walled cysts lined by a continuous layer of epithelium. Although the epithelium may be denuded in a macrocystic serous cystadenoma, it is not accompanied by the pseudocyst-like degenerative changes in the wall. Macrocystic serous cystadenomas are inherently macrocystic and not the result of degenerative change.

15.11.4 Serous Cystic Neoplasm with Complex Florid Papillary Architecture

There is a recent single case report of a serous cystic neoplasm with a peripheral solid nodule, which was composed of a back-to-back arrangement of complex branching papillae (lined by bland, clear, cuboidal, inhibin-immunopositive epithelium) with prominent fibrovascular cores and intervening delicate sieve-like channels [9]. The solid component was mistaken for a neuroendocrine tumor on imaging, and the microscopic florid papillary growth pattern distinguished it from a solid serous adenoma.

15.11.5 Mixed Serous-Neuroendocrine Neoplasm

Very occasionally, serous cystic neoplasms may be associated with a grade 1–3 pancreatic neuroendocrine tumor (PanNET), which may occur either adjacent to the cystic neoplasm or admixed with it. This association is seen most commonly in von Hippel-Lindau syndrome, where the pancreatic endocrine neoplasm is often of clear cell type (see Chap. 20, Sect. 20.12). However, not all patients with a mixed serous-neuroendocrine neoplasm have a genetic syndrome [10].

15.11.6 Serous Cystadenocarcinoma

There are extremely rare reports (approximately 25 in total) of serous cystadenocarcinoma, which was diagnosed on the basis of synchronous or metachronous distant metastases to the liver, peritoneum or (non-peripancreatic) lymph nodes. The morphology of the pancreatic primary and the metastases was similar to that seen in benign serous cystic neoplasms. Hence, clinical behavior appears to be the only way to distinguish serous cystadenomas from serous cystadenocarcinoma. However, it should be noted that primary serous cystadenomas can occur in the liver, albeit rarely [11], and, therefore, liver involvement may represent multifocal disease rather than metastatic malignancy [12].

Locally aggressive growth (such as vascular invasion, perineural invasion, or direct invasion into lymph nodes, spleen, duodenum—Fig. 15.4—or stomach) in a serous cystadenoma does not warrant a diagnosis of malignancy.

15.12 Differential Diagnosis

15.12.1 Metastatic Renal Cell Carcinoma

Metastatic renal cell carcinoma (see Chap. 12, Sect. 12.5 and Table 12.1) may mimic a microcystic serous cystadenoma or a solid serous adenoma. Renal cell carcinoma usually shows nuclear pleomorphism, prominent nucleoli, and mitotic figures, none of which occur in serous neoplasms. Clinical history and immunohistochemistry for vimentin, CD10, renal cell carcinoma marker, and PAX-8 will confirm the diagnosis of renal cell carcinoma (Table 15.1).

15.12.2 Lymphangioma

Lymphangioma (see Chap. 11, Sect. 11.1.7) may be confused with a serous cystic neoplasm, particularly when the epithelial lining is attenuated or denuded in a macrocystic serous cystadenoma. Both entities may contain watery serous fluid. However, lymphangiomas typically have lymphoid aggregates in the cyst wall, do not have a cuboidal epithelial lining and, on immunohistochemistry, express CD31 and D2–40, but not epithelial markers.

Table 15.1 Differential diagnosis of pancreatic clear cell tumors

	PanNET	Metastatic RCC	SCN
Synaptophysin/ chromogranin	++	–	–
NSE/CD56	++	+	++
RCC	–	+/–	–
Vimentin	–	++	–
CAIX	–	++	+
CD10	+	+	–
PAX8	–	++	–

Abbreviations: *PanNET* pancreatic neuroendocrine tumor, *RCC* renal cell carcinoma, *SCN* serous cystic neoplasm
++ usually positive, + may be positive, – usually negative

15.12.3 Clear Cell Pancreatic Neuroendocrine Neoplasm

Clear cell variant of pancreatic neuroendocrine tumors (PanNETs) may mimic a solid serous adenoma macroscopically and microscopically. As discussed above (see Sects. 15.4.1 and 15.11.2), clear cell PanNETs may also coexist with a serous cystic neoplasm, particularly in von Hippel-Lindau syndrome. PanNETs can readily be distinguished from serous cystic neoplasms by immunohistochemistry for chromogranin A and synaptophysin (see Chap. 20, Sect. 20.9.1).

15.12.4 Pseudocyst

Macrocystic serous cystadenoma may be mistaken for a pseudocyst (see Chap. 7, Sect. 7.2.5), particularly when much of the epithelium is denuded. Extensive sampling should reveal residual, cuboidal, clear epithelial cells lining the cysts or entrapped within the wall of the macrocystic serous cystadenoma.

15.12.5 Mucinous Cystic Neoplasm

Mucinous cystic neoplasm (MCN) may mimic a macrocystic serous cystadenoma but MCN typically contains thick mucus, has a thick fibrous capsule, is lined by mucin-producing columnar cells, and has ovarian-type stroma (see Chap. 16). Mucin histochemistry will stain the epithelial lining of a MCN but not a serous cystadenoma. MCNs will also be immunopositive for CEA in contrast to serous cystadenomas, which are negative for CEA.

15.12.6 Intraductal Papillary Mucinous Neoplasm

Branch-duct-type intraductal papillary mucinous neoplasm (Fig. 15.15) may mimic a serous cystadenoma (see Chap. 17). However, intraductal

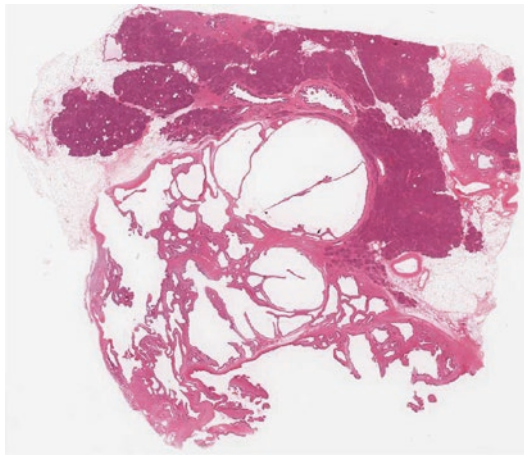

Fig. 15.15 Branch-duct intraductal papillary mucinous neoplasm (IPMN): this small peripheral multilocular cyst was thought to be a serous cystadenoma on macroscopic examination. Microscopy, however, revealed it to be a branch-duct-type IPMN

papillary mucinous neoplasm communicates with the duct system, is lined by papillary mucinous epithelium, and expresses CEA, unlike serous cystadenomas.

15.12.7 PEComa (see Chap. 11, Sect. 11.1.9)

PEComa (perivascular epithelioid cell neoplasm) can occur very rarely in the pancreas and may mimic solid serous adenoma. However, the clear cytoplasm in PEComas is negative for cytokeratins and positive for HMB45, Melan-A, CD31, and smooth muscle actin on immunohistochemistry.

15.13 Prognosis and Management

The prognosis for serous cystic neoplasms is excellent. Most appear to be slow growing and can be followed up clinically. Surgical resection is considered for symptomatic serous cystic neoplasms, for rapidly growing neoplasms, and when it is not possible to definitely exclude a premalignant or malignant cystic tumor such as a mucinous neoplasm [13]. Complete resection (including enucleation) is curative, with less than 2% recurring.

Table 15.2 Reporting checklist for serous cystic neoplasms

Macroscopic assessment
• Specimen type
• Additional resected structures, e.g., spleen
• Tumor location
• Solitary or multifocal (latter suggests von Hippel-Lindau syndrome)
• Tumor size (3-dimensions)
• Cut-surface
• Distance from resection margin(s)
Microscopic assessment
• Microcystic, macrocystic, or solid
• Presence of coexisting pancreatic endocrine neoplasm (suggests von Hippel-Lindau syndrome)
• Extension into adjacent organs or structures (does not equate with malignancy)
• Completeness of excision/resection margin status
• Immunohistochemical profile (if performed)
• Background changes

15.14 Reporting Checklist

A list of macroscopic and microscopic features to consider when reporting a serous cystic neoplasm is shown in Table 15.2.

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Further Reading

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