Benign Tumors and Tumorlike Lesions of the Pancreas

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KEYWORDS

• Benign • Serous • Lymphoepithelial • Squamoid • Epidermoid • Hamartoma • Inflammatory • Pancreatitis

ABSTRACT

The pancreas is a complex organ that may give rise to large number of neoplasms and non-neoplastic lesions. This article focuses on benign neoplasms, such as serous neoplasms, and tumorlike (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. Autoimmune pancreatitis and paraduodenal ("groove") pancreatitis may also lead to pseudotumor formation. Knowledge of these entities will help in making an accurate diagnosis.

OVERVIEW: 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, homogeneous 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 <10) but much larger cysts, each measuring in centimeters. Although "serous cystadenoma (SCA)" and "serous cystic neoplasm (SCN)" terms technically refer to 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 SCNs 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 are 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 computed tomography (CT) or MRI, associated with a central scar that may or may not be calcified, is

The authors have no conflict of interest to declare.
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Surgical Pathology 9 (2016) 619–641
http://dx.doi.org/10.1016/j.path.2016.05.007
1875-9181/16/$ – see front matter

characteristic for *microcystic* variant.[16,17,22,29–31] However, the diagnosis is often not accomplished preoperatively by imaging studies. Similarly, the *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 fine-needle aspiration 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 to 9 and carcinoembryonic antigen (CEA) to identify and distinguish the mucinous neoplasms from nonmucinous lesions, such as serous neoplasms.[40] However, the sensitivity and specificity of these markers are relatively low.[41] Recently, in an enzyme-linked immunosorbent assay analysis of cyst fluid and tumoral tissue, Yip-Schneider and colleagues[42] found that vascular endothelial growth factor-A (VEGF-A) was markedly elevated in SCNs when compared with pseudocysts, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and pancreatic ductal adenocarcinoma. With a cutoff of 8500 pg/mL, VEGF-A had 100% sensitivity and 97% specificity as a marker of SCNs, making it a very promising biomarker for the diagnosis and distinction of SCNs 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 SCN.[41] Molecular assays containing a 5-gene panel may be especially useful in the pretreatment diagnosis of SCNs because 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 SCNs; however, they need to be verified in larger-scale studies before they can be put into daily clinical management.

The mean diameter of SCNs 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* SCNs form partly encapsulated, lobulated masses composed of innumerable tiny cysts, which impart the highly distinctive and entity-defining spongelike appearance on sectioning (**Fig. 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)* SCNs, by definition, are composed of much larger cysts with fewer loculi and devoid of central fibrosis or calcification (**Fig. 2**).

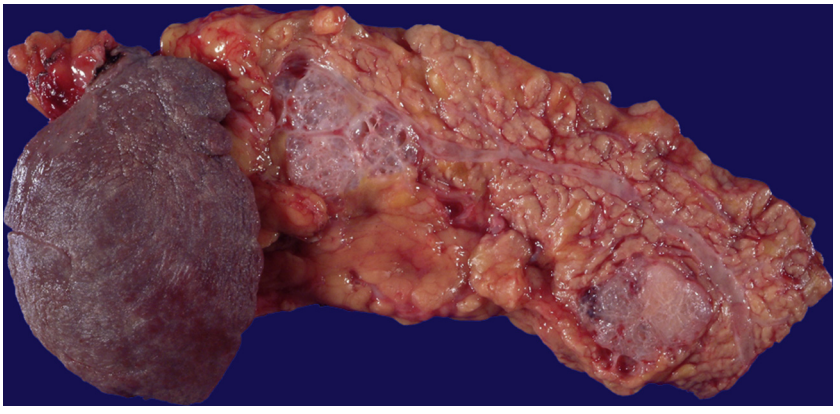

Fig. 1. Two *microcystic* serous cystadenomas are present in this distal pancreas. The neoplasms are well demarcated and composed of numerous small cysts, most of which measure in submillimeters.