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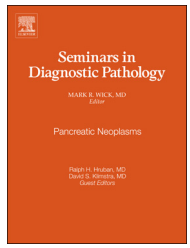

# Serous cystic neoplasms of the pancreas: Clinicopathologic and molecular characteristics

*Michelle D. Reid, MD, Hyejeong Choi, MD, Serdar Balci, MD, Gizem Akkas, MD, Volkan Adsay, MD**

*Department of Pathology, Emory University School of Medicine, Atlanta, GA*

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ABSTRACT

We herein summarize the pathology and most recent advances in the molecular genetics of serous cystic neoplasms of the pancreas. They typically present as relatively large, well-demarcated tumors (mean size, 6 cm), predominantly occurring in females. Pre-operative diagnosis remains challenging; imaging findings and cyst fluid analysis often prove non-specific and fine-needle aspiration often does not yield diagnostic cells. Pathologically, they are characterized by a distinctive cytology referred to as "serous." Although they have ductal differentiation, they distinctly lack the mucin production that characterizes most other pancreatic ductal tumors, including ductal adenocarcinoma and its variants, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). They instead produce abundant glycogen (glycogen-rich adenoma). Serous cystadenomas also lack the molecular alterations that characterize ductal neoplasms, such as mutation of *KRAS* (high prevalence in most mucinous ductal neoplasms), inactivation of *SMAD4* (seen in ductal adenocarcinomas), and mutations in *GNAS* (seen in some IPMNs) and *RNF43* (detected in MCNs and IPMNs). Instead, new molecular and immunohistochemical observations place serous pancreatic tumors closer to "clear cell neoplasms" seen in various other organs that are associated with the von Hippel–Lindau (VHL) pathway, such as clear cell renal cell carcinomas and capillary hemangioblastomas. Patients with VHL syndrome have an increased risk of developing serous pancreatic tumors and somatic mutations of the *VHL* gene are common in these tumors along with modification of its downstream effectors including hypoxia-inducible factor (HIF1), glucose uptake and transporter-1 (GLUT-1), a common factor in clear cell (glycogen-rich) tumors, as well as expression of vascular endothelial growth factor (VEGF), thought to be a factor in the striking capillarization of serous cystadenomas and other non-pancreatic clear cell tumors. VEGF may prove to be of significant diagnostic value since its elevation in cyst fluid has recently been found highly sensitive and specific for serous neoplasms. These molecular alterations establish serous tumors as prototypes of clear cell tumorigenesis and angiogenesis and may prove helpful both as diagnostic and non-surgical therapeutic targets.



* *Correspondence to*: Department of Pathology and Laboratory Medicine, Emory University Hospital, 1364 Clifton Road NE, Room H-180B, Atlanta, GA 30322.
E-mail address: nadsay@emory.edu (V. Adsay).

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## Introduction

Serous cystic neoplasms (SCNs) of the pancreas are rare primary pancreatic tumors comprising less than 1% of all pancreatic lesions. The cysts are lined by cuboidal or flattened non-mucinous epithelium containing abundant glycogen [periodic acid–Schiff (PAS)-positive, diastase-sensitive], which imparts a characteristic clear appearance to the cells and is associated with a complex capillary meshwork.[1] These tumors were first classified as a distinct entity by Compagno and Oertel[2] and Hodgkinson et al.[3] Since then several studies have elucidated their trademark benign behavior, especially in contrast with ductal neoplasms of a mucinous nature, which are typically either malignant or pre-cancerous.

Sporadically occurring serous cystic neoplasms (SCNs) are far more frequent than those arising in von Hippel–Lindau (VHL) syndrome, an extremely uncommon, autosomal dominant multi-organ syndrome characterized by germline mutations in the *VHL* tumor suppressor gene. VHL syndrome affects 1 in 36,000 live births and has very high penetrance (>90%) by the age of 65 years.[4,5] Affected patients develop tumors of the central nervous system (hemangioblastoma), retina (angioma), epididymis (cystadenoma), adrenal glands (pheochromocytoma), kidneys (cysts and clear cell renal cell carcinoma), and pancreas (neuroendocrine tumors and serous cystadenomas).[5–8] The *VHL* gene is located on the short arm of chromosome 3 (3p25–3p26)[9] and encodes for two isoforms of pVHL (a 213-amino acid and a 160-amino acid form).[10] Altered VHL protein leads to a buildup of hypoxia-inducible factors (HIF-1α and HIF-2α), which are cell proteins involved in angiogenesis, cell proliferation, survival, and glucose metabolism.[11] Interestingly, many of the tumors that arise due to alteration of this pathway have striking vascularity and glycogen-rich (clear) cells.

At least five morphologic subtypes of SCN are described. These include (1) serous cystadenoma (microcystic and macrocystic/oligocystic), (2) solid serous adenoma, (3) VHL-associated serous cystic neoplasm, (4) serous cystadenocarcinoma, and (5) mixed serous–neuroendocrine neoplasms. Regardless of subtype the distinctive clear cells and uniform tumor nuclei are usually maintained. While the histomorphologic observations in SCNs have changed little over the years, our understanding of the immunoprofile and the molecular abnormalities that characterize these neoplasms has advanced significantly in recent years. We herein describe the clinicopathologic features of these unusual tumors and review recent advances in the literature concerning their diagnosis and genetics.

## Clinical and pathologic features

SCNs are most frequently seen in females (F:M > 2.5:1).[12,13] Patients typically present in the seventh decade and have a mean age of 60–65 years; however, these tumors have a wide age distribution.[12–14] The microcystic variant is more common in females and favors the pancreatic tail. Although the literature has previously reported that the macrocystic variant, is more common in men and the pancreatic head, in our recent analysis we found the macrocystic variant to be very similar to microcystic SCNs, occuring predominantly in the pancreatic tail of females. Solid serous adenomas are less common and relatively less characterized, do not appear to show any gender predilection, and can be found anywhere in the pancreas.[8,15,16] VHL-associated tumors have no sex predilection and often arise as multifocal tumors in younger patients.[7,17,18]

Small SCNs are usually discovered incidentally, while large SCNs can cause symptoms. Symptoms include abdominal or epigastric pain, dyspepsia, nausea, vomiting, jaundice, or a palpable abdominal mass.[12,13] Up to 80% of patients are asymptomatic at diagnosis, and these tumors are discovered incidentally when imaging is performed for other reasons.[12] With the advent of non-surgical treatment options such as ethanol, paclitaxel, and radiofrequency ablation, accurate presurgical diagnosis of SCNs is especially critical.[19–21]

### *Pre-operative diagnosis*

#### *Imaging studies*

On computerized tomography scan, microcystic SCNs have a classical honeycomb, soap-bubble appearance with a central stellate scar (visible in only 20% of cases)[22] that may or may not be calcified. The presence of calcification may mimic a neoplastic mucinous cyst [intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN)] or pseudocyst.[12,23–25] Cyst locules are separated by thin fibrous septae and lesions can appear hypervascular.[1,26] The radiologic misdiagnosis of SCNs occurs more frequently with the macro/oligocystic variant.[27] In one study only 23% of all SCNs were accurately diagnosed on computed tomography (CT).[24] The solid variant may be misdiagnosed on imaging as pancreatic neuroendocrine tumors or solid pseudopapillary neoplasms. There are also very rare reports of SCNs communicating with the ductal system, a feature that makes their radiologic distinction from IPMN even more challenging.[28–31]

#### *Fine-needle aspiration biopsy*

Fine-needle aspiration (FNA) has limited utility in the diagnosis of SCNs, a particularly vexing issue for cytopathologists and gastroenterologists alike. The diagnostic sensitivity of FNA is very low and may be less than 20% in some cases, because of acellular or paucicellular aspirates.[32–36] CT-guided biopsies yield more cellular material than endoscopic ultrasound-guided aspirates, presumably because they use comparably larger needles (18-gauge versus 22-gauge).[34,37] In specimens with diagnostic material the cellularity is low to moderate. Smears are composed of sheets and singly dispersed bland cuboidal-to-low columnar cells containing clear cytoplasm and round to oval nuclei with even granular chromatin.[33–35,37] The neoplastic cells may express α-inhibin (seen in 88% of SCNs in a recent cytologic series), which may improve diagnostic accuracy.[35] Unfortunately smears and cell blocks are often acellular in SCNs, which makes the diagnostic utility of immunohistochemistry limited.[33,34]

#### *Cyst fluid analysis*

With increased sensitivity of imaging studies, incidentally discovered pancreatic cysts are on the rise.[13] Most are low-