

# Is Serous Cystadenoma of the Pancreas a Model of Clear-Cell-Associated Angiogenesis and Tumorigenesis?

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## Key Words

Pancreas · Serous cystadenoma · Angiogenesis · Clear cell

## Abstract

**Background:** Similar to the other von Hippel-Lindau (VHL)-related tumors such as renal cell carcinomas and capillary hemangioblastomas, serous cystadenomas (SCAs) of the pancreas are also characterized by clear cells. Over the years, we have also noticed that the tumor epithelium shows a prominent capillary network. **Methods:** Eighteen cases of SCA were reviewed histologically, and immunohistochemical analysis was performed for CD31 and vascular endothelial growth factor (VEGF) as well as the molecules implicated in clear-cell tumorigenesis: GLUT-1, hypoxia-inducible factor-1 (HIF-1 $\alpha$ ), and carbonic anhydrase IX (CA IX). **Results:** There was an extensively rich capillary network that appears almost intraepithelially in all cases of SCA, which was confirmed by CD31 stain that showed, on average, 26 capillaries per every 100 epithelial cells. VEGF expression was identified in 10/18 cases. Among the clear-cell tumorigenesis markers, CA IX was detected in all cases, GLUT-1 and HIF-1 $\alpha$  in most cases. **Conclusion:** As in other VHL-related clear-cell tumors, there is a prominent capillary network immediately adjacent to the epithelium of SCA, confirming that the clear-cell-angiogenesis association is also valid for this tumor type.

Molecules implicated in clear-cell tumorigenesis are also consistently expressed in SCA. This may have biologic and therapeutic implications, especially considering the rapidly evolving drugs against these pathways. More importantly, SCA may also serve as a model of clear-cell-associated angiogenesis and tumorigenesis, and the information gained from this tumor type may also be applicable to other clear-cell tumors.

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## Introduction

Serous cystadenoma (SCA) of the pancreas, also named clear-cell or glycogen-rich adenoma because of the abundance of intracytoplasmic glycogen [1–6], is a peculiar and distinctive tumor, by both morphologic characteristics and biologic behavior. It is the only nonmucinous example of ductal neoplasia in this organ, presumably originating from the centroacinar cells [5, 7–9]. Furthermore, unlike other ductal tumors, SCA has only negligible, if any, tendency for malignant transformation [10–13].

It appears to be the sporadic/tumoral version of von Hippel-Lindau (VHL)-associated cysts in the pancreas and is morphologically identical to VHL-associated cysts displaying the same type of clear cells but instead forms

discrete tumors while the latter is characterized by irregularly distributed cysts in the pancreas [14]. VHL gene alterations have also been identified in more than 40% of the cases with SCAs, even when tested with relatively insensitive methods [15–17].

SCA also has many similarities to the clear-cell tumors of other organs, namely renal cell carcinoma and capillary hemangioblastoma, which have a well-established association to VHL [18–20]. As SCA, both renal cell carcinoma and capillary hemangioblastoma are characterized by glycogen-rich cells that have abundant clear cytoplasm and distinct cytoplasmic borders. Their well-known association with prominent vascularity is important biologically and for treatment protocols [21]. Some of the recently identified molecular events in the tumorigenesis of renal cell carcinoma and capillary hemangioblastoma such as the role of glucose uptake and transporter-1 (GLUT-1) and carbonic anhydrase IX (CA IX) are also interesting. GLUT-1 has been found to have an important role in the upregulation of various cellular pathways and neoplastic progression [22–30]. CA IX, also called renal cell carcinoma-associated protein because of its consistent and fairly specific expression in renal cell carcinoma [31–37], is known to have a role in the regulation of hydrogen ion (H<sup>+</sup>) flux and considered a reliable marker of hypoxia [38]. Another hypoxia-associated factor, hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), which has been found to have a role in clear-cell tumorigenesis, was also investigated.

In this study, the striking phenomenon of neo-angiogenesis and other aspects of clear-cell-associated tumorigenesis in SCAs are documented and the potential implications of these findings are discussed.

## Material and Methods

The pancreatic surgical database of Wayne State University and Karmanos Cancer Institute and the consultation database of one of the authors (N.V.A.) were searched for SCAs. The surgical pathology reports and the slides of these cases were retrieved.

Patients' demographic data (age and gender), tumor size, tumor location and the macroscopic findings of the tumors were extracted from the reports. Clinical findings of the cases were obtained through contact with the primary physicians or review of patients' hospital charts.

Immunohistochemical analysis was performed for vascularity (CD31), neo-angiogenesis (vascular endothelial growth factor, VEGF), and molecules recently implicated in the tumorigenesis of other clear-cell tumors (GLUT-1, HIF-1 $\alpha$ , and CA IX) on randomly selected blocks that contained abundant tumor. Routine streptavidin-biotin technique with no biotin blocking was used. Negative and positive controls were included with each

**Table 1.** Summary of immunohistochemical antibodies

Antibody	Source	Clone	Titration	Pretreatment
CD31	Ventana	JC70A	Predilute	CC1 benchmark
VEGF	Santa Cruz	N/A	1:50	Protease 1 6 min
GLUT-1	Dako	35310	1:100	Citrate-steam
CA IX	Novus	G250	1:400	CC1 benchmark
HIF-1 $\alpha$	Novus	H1alpha67	1:1,000	CC1 benchmark

batch of slides tested. Primary antibodies, their sources, dilutions and antigen retrieval methods for each are listed in table 1.

### Evaluation of Immunohistochemistry

*Vascularity Analysis with CD31.* The distribution of capillaries was noted, and the number of capillaries/100 epithelial cells was counted. A capillary was defined as one completely encircled vascular space highlighted by CD31 immunostain.

*Other Antibodies.* Labeling in the cells was graded as positivity 0, 1, 2 and 3 regarding the intensity and the percentage of the staining in each case (grade 0 = <5% of total cell population; grade 1 = weak staining, 5–50% of total cell population; grade 2 = weak staining, >50% of total cell population or strong staining, 5–50% of total cell population; grade 3 = strong staining, >50% of total cell population).

*Statistical Analysis.* Pearson correlation coefficients and Student's t test were used to test the relationship between number of capillaries and VEGF expression as well as between size of the tumor and VEGF expression. The same tests and conditions were also applied for the correlation of GLUT-1 expression.

## Results

Among 1,499 cases with pancreatic tissue in the database, 18 cases of SCA on whom adequate material and information available were identified. These were 12 females and 6 males with mean age = 59 (range 31–78). Mean size of the tumors was 4.5 cm (range 1.5–15 cm). Sixteen tumors were classical microcystic type, and 2 tumors were oligocystic type. The majority of the tumors were located in the body or tail; only 2 were in the head. One case had two separate lesions. Five women had incidental hepatic cysts, but genetic information was not available in any of the patients for mutations in the VHL gene or allelic losses on chromosome 10q, which is the most frequent molecular event in sporadic SCAs as reported by Moore et al. [15]. The presenting symptoms were abdominal pain in 6 cases, nausea and vomiting in 2 cases and weight loss in 1 case. Three cases were detected incidentally during work-up for other diseases

**Table 2.** Summary of the immunohistochemical studies

Case	Age	Sex	Tumor size	Capillary concentration <sup>1</sup>	CD31	VEGF	GLUT-1	CA IX	HIF-1 $\alpha$
1		F	N/A	19.20	2	0	2	2	2
2	31	F	3	12.20	3	0	0	3	2
3	37	F	N/A	18.75	3	0	2	3	2
4	59	M	4.5	33.20	3	2	1	3	3
5	78	F	3.5	22.91	3	3	3	3	3
6	75	F	5.5	21.85	3	2	1	3	2
7	74	F	6.5	30.90	3	3	3	3	3
8	63	M	5.3	28.73	3	2	3	3	3
9	62	F	15	23.44	3	0	3	3	2
10	39	M	3.5	27.88	3	2	2	3	2
11	38	M	2.5	24.36	3	0	3	3	2
12	67	F	3.5	15.60	3	2	3	3	2
13	75	F	2	36.84	3	3	3	3	3
14	67	F	N/A	52.63	3	0	2	3	3
15	78	M	3.0, 4.0	21.00	3	2	3	3	3
16	40	F	1.5	25.00	2	0	2	3	2
17	46	F	3.5	19.59	3	2	2	3	1
18	77	M	N/A	35.45	3	0	3	3	3

0 = <5% of total cell population; 1 = weak staining plus 5–50% of total cell population; 2 = weak staining plus >50% of total cell population or strong staining plus 5–50% of total cell population; 3 = strong staining plus >50% of total cell population. N/A = Not applicable.

<sup>1</sup> Number of capillaries per 100 epithelial cells.

(1 for staging prostatic cancer, 1 for bilateral breast cancer and 1 for colonic cancer).

#### *Pathologic Findings*

All tumors exhibited the characteristic well-described features of SCAs. Macroscopically, they were relatively well-demarcated tumors with sponge-like configuration due to the presence of numerous tightly packed glandular units (fig. 1). Microscopically, the low cuboidal tumor cells with glycogen-rich clear cytoplasm were intimately admixed with capillaries (fig. 2). No tall papillary structures, no necrosis, mitotic activity or any evidence of malignancy was identified. In 4 cases, incidental PanIN-1 was noted.

#### *Hypervascularity in Serous Cystadenoma*

There was an extensively rich capillary network in all tumors, which was readily evident even by routine HE stain. This network was so intimately admixed with the epithelium that it gave the impression to be intraepithelial. This was manifested by the presence of numerous red blood cells, which seemed interspersed between the epithelial cells (fig. 2). The remarkable intensity of this vas-

cularity was highlighted also by CD31 stain (fig. 3). There were, on average, 26 capillaries per every 100 epithelial cells (range, 12–53). This hypervascularity was limited to epithelial area; no other significant hypervascularity or selective vascular distribution was identified in the interstitium, at the periphery of the tumor or outside the tumor area.

**Fig. 1.** Well circumscribed, bosselated round lesion with polycystic and honey comb-like cut surface, showing numerous cysts in various size.

**Fig. 2.** The low cuboidal tumor cells with clear cytoplasm are intimately admixed with the prominent capillary network (fig. 3).

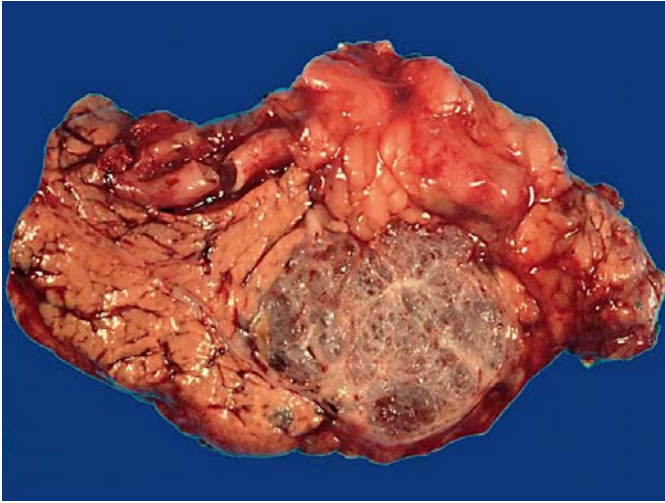
**Fig. 3.** CD31 discloses both the abundance of capillaries and their preferential distribution around the epithelial cells.

**Fig. 4.** VEGF stain shows strong and consistent positivity in both cell membrane and cytoplasm. This was seen in 10/18 cases.

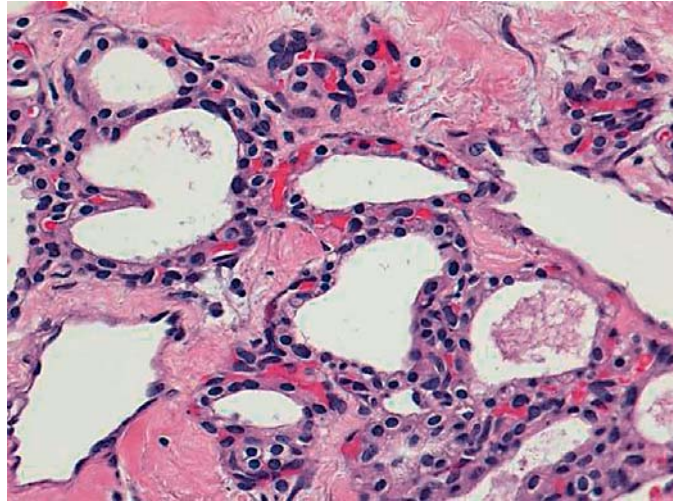
**Fig. 5.** GLUT-1 was expressed diffusely in almost all cases. The staining accentuates the membranes, but cytoplasmic labeling is also present.

**Fig. 6.** CA IX, a good marker of clear cell tumors, was expressed in all cases, with mostly membranous labeling.

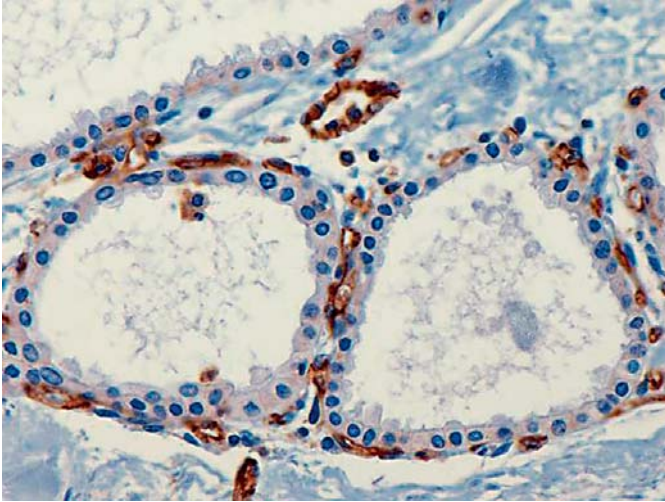
1



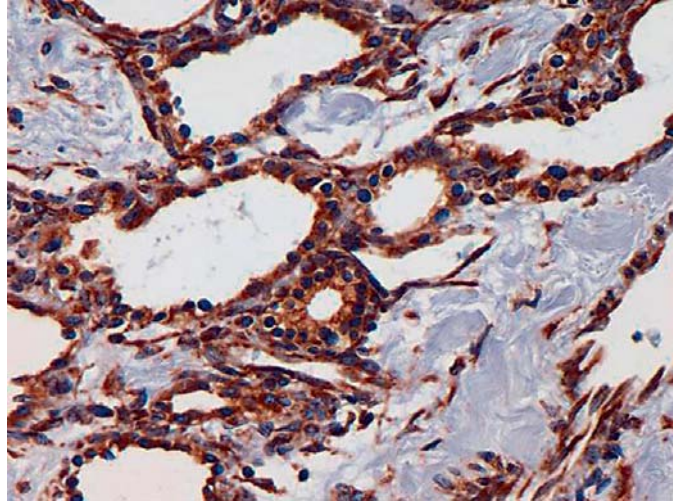
2



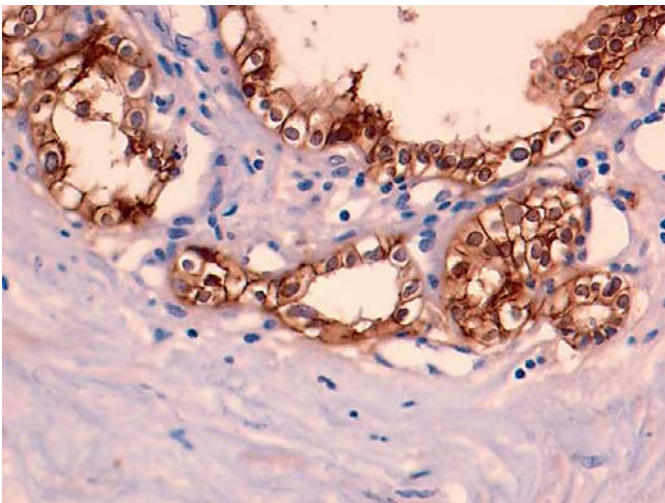
3



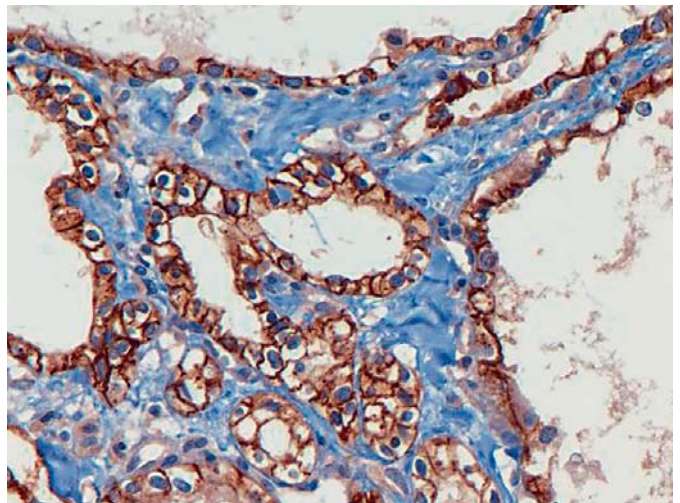
4

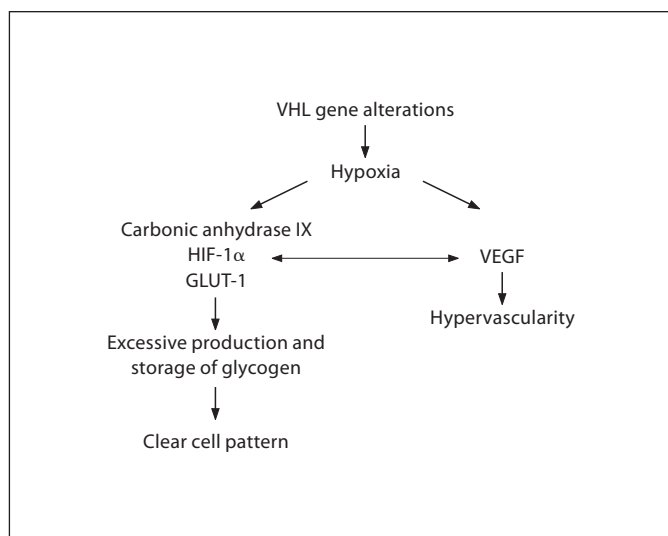


5



6





**Fig. 7.** Diagram shows the model of clear-cell tumorigenesis and angiogenesis.

### *Neo-Angiogenesis*

In 10 cases, VEGF expression was detected in the cell membranes and cytoplasm; in 3 of these, the labeling was grade 3 (fig. 4). There was no statistical correlation between number of capillaries and VEGF expression. Also, there was no statistical correlation between tumor size and VEGF expression.

In 17 cases, GLUT-1 expression was detected predominantly in the cell membranes, but also in the cytoplasm; in 9 of these, the expression was grade 3 (fig. 5). There was no statistical correlation between GLUT-1 expression and degree of vascularity or the tumor size.

CA IX and HIF-1 $\alpha$  expressions were detected in all SCAs with 17 and 8 cases showing grade 3 labeling, respectively. As expected, these molecules were expressed in the cell membranes (fig. 6).

The results are summarized in table 2.

### **Discussion**

This study elucidates that SCA is indeed a markedly hypervascular tumor, confirming the observation recently made by Yamazaki et al. [39] in an analysis of 4 cases studied by electron microscopy. We have also noticed that an exuberantly rich capillary network immediately adjacent to the epithelium is readily evident even by routine HE stain in larger series of SCA. This finding fur-

ther accentuates the kinship of SCA with other clear-cell tumors, namely renal cell carcinoma and capillary hemangioblastoma, which are notorious for being highly vascularized tumors, in addition to their association with VHL [18–20, 40].

This vascularity may have potential diagnostic implications. With the advances in radiologic methods, it is expected that it will become increasingly more feasible to detect this kind of vascularity at the radiologic level. The rich capillary network may also be helpful for surgical pathologists, especially as needle biopsies are becoming the norm for initial work-up of the patients. In fact, the authors used this as a confirmatory finding in 2 recent biopsies with substantial crush artifact influencing the morphology of the cells but retaining the vascularity. This finding may also be helpful in frozen sections where clear-cell cytology is typically not evident due to the preservation of glycogen.

Additionally, VEGF expression in SCA might have therapeutic implications. In our study, more than half of SCA was found to express VEGF at the immunohistochemical level. Therefore, VEGF itself may serve as a potential target for anti-angiogenic therapy [41–44] in the management of SCAs, especially in patients in whom surgery is contraindicated. Currently, most SCAs are resected because preoperative diagnosis of this benign tumor is not reliable. However, some patients undergo resection despite the definitive preoperative work-up because either the tumor is symptomatic or grows rapidly. Recent data indicate that an important portion of SCAs have a short doubling time of few months [45, 46] and some authors recommend resection for large (>4 cm) serous cystadenomas regardless of the presence or absence of symptoms [46]. In such cases, if the preoperative diagnosis is established, anti-VEGF or other anti-angiogenic approaches would be a consideration.

More importantly, this study demonstrates that the similarities of SCA to other clear-cell tumors are even more so than previously recognized hypervascularity. They also express the same immunohistochemical markers such as GLUT-1, CA IX and HIF-1 $\alpha$ . Potentially, the new information obtained from this tumor type will be applicable to its kindreds and vice versa. Thus, SCA may serve as a model of clear cell tumorigenesis and angiogenesis presumably related to VHL gene alterations that lead to hypoxia. This, in turn, leads to the activation of a cascade of events including VEGF, GLUT-1, CA IX and HIF-1 $\alpha$ , ultimately resulting in the distinct clear-cell pattern of these tumors and their peculiar hypervascularity. Accordingly, with these findings, a new hypothesis on the

pathogenesis of SCA also crystallizes (fig. 7). It appears that the cells involved in SCA fall into the perception that they are undergoing hypoxia. As an attempt to recover from this perceived hypoxia, they recruit new blood vessels and form an exuberant vascular network; and also activate the pathways that lead to the excessive production and storage of glycogen.

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