

Solid Serous Cystadenoma of the Pancreas: A Case Report of 2 Patients Revealing Vimentin, β -Catenin, α -1 Antitrypsin, and α -1 Antichymotrypsin as New Immunohistochemistry Staining Markers

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Abstract: Solid serous cystadenoma (SCA) of the pancreas is a rare type of pancreatic solid tumors. Postoperative pathological evaluation is of particular importance for distinguishing solid SCA of the pancreas from other pancreatic solid tumors.

Here we present 2 cases of solid SCA of the pancreas, both preoperatively diagnosed with pancreatic neuroendocrine tumors. One case had positive OctreoScan test.

Surgical resections were done for both cases. Postoperative immunohistochemistry assays were conducted with marker panels for SCA and 2 types of pancreatic solid tumors, which were neuroendocrine tumor (pNET) and solid pseudopapillary tumor (SPT).

Two cases showed typical staining patterns for SCA markers. Notably, both cases showed positivity for 4 SPT markers (vimentin, β -catenin, α -1 antitrypsin, and α -1 antichymotrypsin).

Emphasis should be paid to those 4 new markers for future pathological diagnosis of solid SCA of the pancreas.

(*Medicine* 94(12):e644)

Abbreviations: IHC = immunohistochemistry, PAS = periodic acid–Schiff, pNET = pancreatic neuroendocrine tumor, SCA = serous cystadenoma, SPT = solid pseudopapillary tumor, SSCA = solid-type serous cystadenoma.

INTRODUCTION

Serous cystadenoma (SCA) of pancreas accounts for more than half of cyst-forming neoplasms and has been increasingly recognized with advancement of clinical imaging

evaluations.¹ Its biological behavior is benign compared with other types of cyst-forming neoplasms, including mucinous cystic neoplasms and intraductal papillary mucinous neoplasms. Under the light microscope, tumor cells of SCA are polygonal in shape with small round nuclei and clear or pale cytoplasm, usually without mitosis or necrosis. The cytoplasm consists of glycogen granules, which are periodic acid–Schiff (PAS) positive but diastase sensitive. Tumor cells are organized in patterns of solid/nested, microcystic, or oligocystic architecture.² Immunohistochemistry (IHC) typically shows positivity for epithelial marker protein cytokeratin 7/8/18/19 and epithelial mucin 1/6, α -inhibin.³

Solid-type serous cystadenoma (SSCA), which was originally designated by Perez-Ordóñez et al,⁴ is an extremely rare disease entity with only 15 cases reported so far.⁵ Apart from other subtypes of SCA with cyst morphology, SSCA is a solid pancreatic tumor. The preoperative diagnosis of SSCA is rather challenging and often misdiagnosed as other solid pancreatic tumors.⁵

Here we present 2 cases of SSCA. We screened the IHC markers for SCA and 2 types of solid pancreatic tumors that are solid pseudopapillary tumor (SPT) and pancreatic neuroendocrine tumor (pNET). Unexpectedly, 4 SPT markers were positive for both SSCA cases, which were vimentin, β -catenin, α -1 antitrypsin, and α -1 antichymotrypsin.

CLINICAL PRESENTATION

Case 1

A 48-year-old male presented with episodes of severe left abdominal cramps, without nausea and vomiting. The past medical history was significant for hypercholesterolemia and multiple kidney cysts. Physical examination was unremarkable. Preoperative contrast-enhanced computed tomography revealed a 2.7 cm, round mass in the head of the pancreas with enhancement in the arterial phase (Figure 1A) and 3 ring-enhancing mass in liver segments V and VIII ranging from 1.5 to 1.9 cm in diameter with obscure boundaries to the surrounding liver parenchymal. An OctreoScan test detected hot spots in the head of the pancreas and the right lobe of liver (Figure 1B). Based on the evidence of typical computed tomography imaging pattern and positive OctreoScan test, the preoperative diagnosis was pNET with probable liver metastasis. The patient underwent pyloric-preserving pancreaticoduodenectomy with cholecystectomy to resect the pancreatic tumor. However, the tumors in the liver were not resected because the patient insisted on not removing them. No subsequent radiotherapy or chemotherapy was conducted. Follow-up was conducted 2 years later

Editor: Shefali Agrawal.

Received: December 8, 2014; revised: February 3, 2015; accepted: February 20, 2015.

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WWu, XH, and JL have contributed equally to this article as co-first authors. The authors have no funding and conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000644

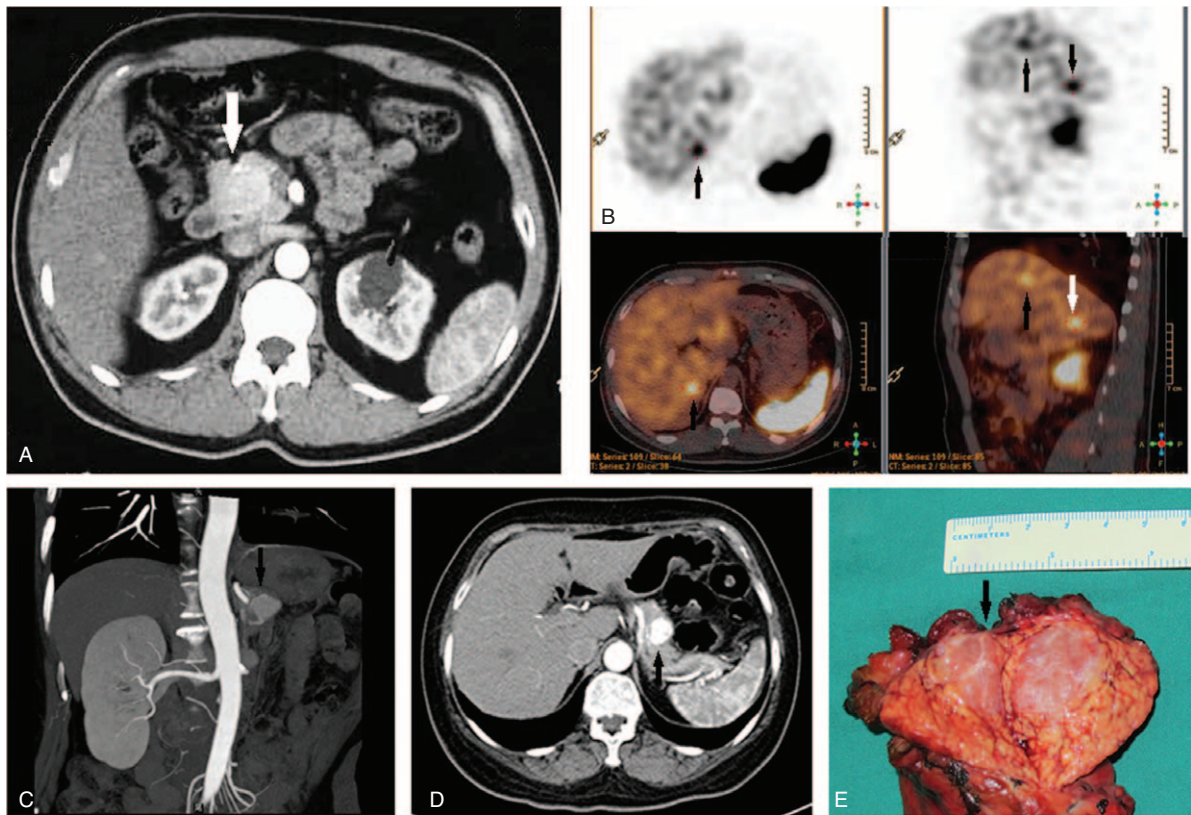


FIGURE 1. Preoperative imaging studies for serous cystadenoma of pancreas (arrow indicates the location of tumor mass). (A) Arterial-phase enhancing mass in the head of the pancreas by computed tomography for Case 1. (B) OctreoScan revealed 3 masses in the liver for Case 1. (C) 3D reconstruction imaging of a mass to the left side of the abdominal aorta for Case 2. (D) Arterial-phase enhancing mass in the body of the pancreas by computed tomography for Case 2. (E) Gross appearance for specimen for Case 1.

showing no evidence of pancreatic tumor recurrence and the size of liver tumors were the same as previous.

Case 2

A 65-year-old female was found to have a 2.3 × 1.8cm, round, arterial-phase enhancing mass in the body of the pancreas by computed tomography (Figure 1C and D). The past medical history was significant for breast cancer and hypertension. Physical examination was unremarkable. OctreoScan test was not conducted. The preoperative diagnosis was pNET, based on the typical computed tomography imaging pattern. The patient underwent laparoscopic spleen-preserving distal pancreatectomy, without subsequent radiotherapy or chemotherapy.

METHODS

Ethical Approval

This study was approved by the Institutional Review Board of the Peking Union Medical College Hospital, Beijing, China. Both patients signed the informed consents to approve the use of surgical specimen for research purposes.

Staining Protocol

The IHC staining was conducted in the Department of Pathology, Peking Union Medical College Hospital. The IHC markers were stained by automated IHC/ISH (immunohistochemistry/in situ hybridization) staining instrument (Ventana,

Mountain View, CA, USA), according to the standardized protocol.

PATHOLOGICAL ANALYSIS

Both cases had firm, gray–pink, well-demarcated tumor masses with adjacent normal pancreas tissues harvested during the surgery. The tumor size of Case 1 measured 22 × 18 × 18 mm (Figure 1E) and that of Case 2 measured 18 × 10 × 10 mm. Histologically, both tumors consisted of cells with small round nuclei and clear cytoplasm (Figure 2A and B). Both tumors had solid area of nested cells, whereas other parts of the tumor showed microcystic morphology with cells of lobular architecture. Fibrous tissues could be seen between the tumors and the adjacent normal pancreas, and between the tumor nests and lobules. Both tumors were PAS positive and diastase sensitive. Immunohistochemistry assay was conducted with a list of markers, which could potentially differentiate SCA, pNET, and SPT. The SCA panel included cytokeratin 7/19, AE1/AE3, epithelial membrane antigen, and α-inhibin.³ The pNET included chromogranin A, synaptophysin, carcinoembryonic antigen, and endocrine peptides (insulin, glucagon, serotonin, gastrin, calcitonin, and somatostatin).⁶ The SPT panels included CD56, CD10, vimentin, α-1 antitrypsin, α-1 antichymotrypsin, progesterone receptor, and β-catenin.^{7–10} Both cases showed positivity for all SCA panel markers and negativity for all pNET panel markers, except for the negativity of α-inhibin in Case 2 (Table 1). As for the SPT panels, both

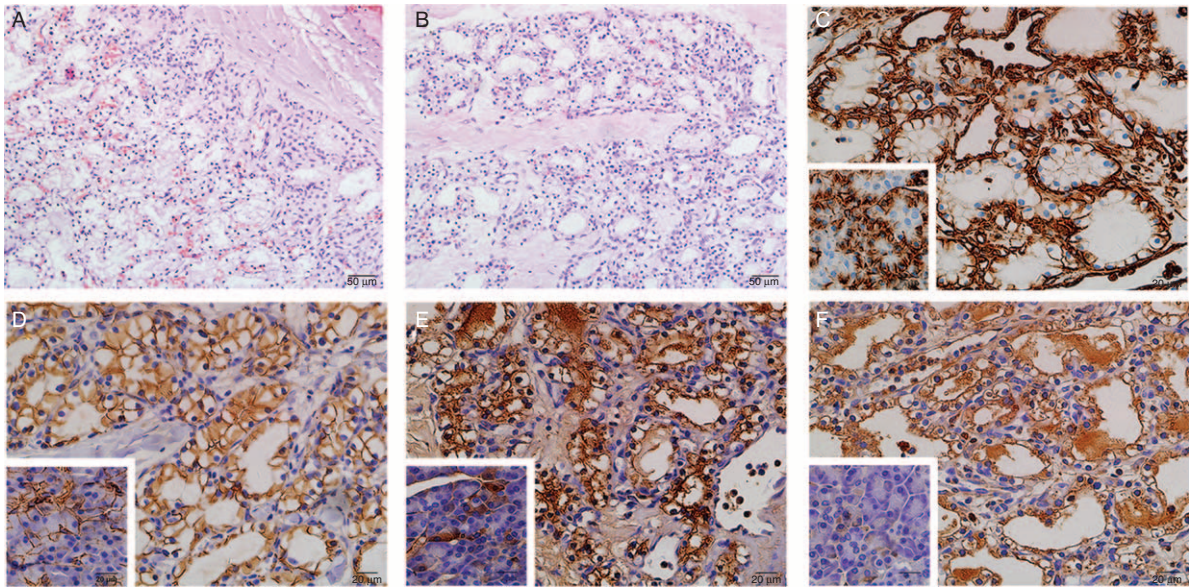


FIGURE 2. Pathological staining for serous cystadenoma of pancreas. (A) H&E stain for Case 1. (B) H&E stain for Case 2. (C) Vimentin staining pattern for the tumor for Case 1, the left bottom panel indicated normal pancreas acinar cell as control. (D) β -Catenin staining pattern for the tumor for Case 1, the left bottom panel indicated normal pancreas acinar cell as control. (E) α -1 Antitrypsin staining pattern for the tumor for Case 1, the left bottom panel indicated normal pancreas acinar cell as control. (F) α -1 antichymotrypsin staining pattern for the tumor for Case 1, the left bottom panel indicated normal pancreas acinar cell as control. H&E = hematoxylin and eosin.

cases showed strong positivity for vimentin on the basal membrane, weak positivity for the lateral membrane, and negativity on the apical membrane of the tumor cell, without cytoplasmic or nuclear staining (Figure 2C). Both cases showed strong positivity for β -catenin with membranous localization (Figure 2D). Both cases also showed positivity for α -1 antitrypsin and α -1 antichymotrypsin, which were localized primarily in cytoplasm of tumor cells and the lumen surrounded by tumor cells (Figure 2E and F). Both of them were negative for CD56, CD10, and progesterone receptor. The staining patterns mentioned above were similar in both solid and microcystic areas of the tumors.

DISCUSSION

SSCA is relatively rare compared with microcystic and oligocystic counterparts. The underlying pathophysiological and molecular differences among solid, microcystic, and oligocystic components are still unknown. Whole-exome sequencing of SCA has revealed only 10 somatic mutations for each SCA, much less than pancreatic adenocarcinoma.¹¹

The diagnosis of SSCA is challenging by routine clinical imaging studies. The 2 cases in the present study demonstrated similar properties with pNET by contrast-enhanced computed tomography. Of note, 1 case even showed positivity for OctreoScan, which was thought as a specific study for neuroendocrine tumors with somatostatin receptors.

From our perspective, although preoperative biopsy is rarely done for suspected pancreatic neuroendocrine tumors, postoperative pathological confirmation of the definitive diagnosis is a routine practice.

SCA carries good prognosis. Either surgery or observation is acceptable for SCA, and no further targeted or chemotherapy is necessary.¹ Targeted therapy, such as everolimus, is an option for advanced pNET.¹²

The pathological examination and staining patterns in these 2 cases were typical for SSCA. The markers for pNET were exclusively negative, which demonstrated that pathological workup could serve as a reliable tool to differentiate SSCA from pNET. Unexpectedly, SPT markers (vimentin, β -catenin, α -1 antitrypsin, and α -1 antichymotrypsin) were positive in these 2 cases. Vimentin is a type of intermediate filament and a marker for mesenchyme cell origin. Previous studies demonstrated that vimentin played a role in epithelial to mesenchymal transitions.^{13,14} The typical staining pattern of vimentin for SPT is cytoplasmic and membranous localization.⁷ SCA was originally considered to be stained negative for vimentin.³ However, a recent case report suggested membranous vimentin positivity for microcystic SCA.¹⁵ Our results showed a similar pattern of membranous vimentin positivity in both the cases. The membrane-localized β -catenin functions as a member of E-cadherin- β -catenin- α -catenin complex for cell-cell adhesion, whereas the nuclear-localized counterparts alter gene expression and are involved in epithelial to mesenchymal transitions.¹⁶ The typical staining pattern of β -catenin in SPT was nuclear and cytoplasmic.¹⁰ We demonstrate that, in contrast to SPT, the β -catenin is exclusively stained positive on the membrane of SSCA. α -1 antitrypsin and α -1 antichymotrypsin are both acute-phase proteins, which are focally positive in SPT.⁷ The 2 cases of SSCA showed cytoplasmic localization of the 2 markers, and more significantly, the lumen of the SSCA also showed positive stain. This indicates that α -1 antitrypsin and α -1 antichymotrypsin may be produced by and secreted from the tumor cells of SSCA.

We admitted that the underlying molecular basis for SSCA has not been yet uncovered. Unlike other subtypes of SCA, SSCA does not have cysts, but why? The 4 newly identified markers by themselves could not fully explain those questions. Given that vimentin and β -catenin localized on the membrane, we inferred that the cell-cell adhesion by these molecules were

TABLE 1. Pathological Staining for 2 Solid-Type SCA Cases

Panels	Antibody	Case 1	Case 2
SCA	PAS	Positive	Positive
	PAS diastase	Sensitive	Sensitive
	Cytokeratin 7/19	Positive	Positive
	AE1/AE3	Positive	Positive
	EMA	Positive	Positive
pNET	α -Inhibin	Positive	Negative
	CgA	Negative	Negative
	Syn	Negative	Negative
	CEA	Negative	Negative
	Insulin	Negative	Negative
	Glucagon	Negative	Negative
	Serotonin	Negative	Negative
	Gastrin	Negative	Negative
SPT	Calcitonin	Negative	Negative
	CD56	Negative	Negative
	CD10	Negative	Negative
	Vimentin	Positive	Positive
	α -1 Antitrypsin	Positive	Positive
	α -1 Antichymotrypsin	Positive	Positive
	Progesterone receptor	Negative	Negative
β -Catenin	Positive	Positive	

CEA = carcinoembryonic antigen, CgA = chromogranin A, EMA = epithelial membrane antigen, pNET = pancreatic neuroendocrine tumor, SCA = serous cystadenoma, SPT = solid pseudopapillary tumor, Syn = synaptophysin.

at least not absent in SSCA. We expect future research to address the difference between SSCA and other types of SCA to a greater extent and depth.

ACKNOWLEDGMENTS

The authors would like to thank Wenyang Qiu and Xiaojing Qian from the Department of Anatomy, Histology, and Embryology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, Beijing, China, for their kind support for capturing high-quality images from the immunohistochemistry staining slides. They would also like to thank Yijia Li and Rui Tian from Peking Union Medical College for language editing.

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