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【 CASE REPORT 】

Metachronous Pancreatic Ductal Adenocarcinoma with Adjacent Serous Cystadenoma that Was Preoperatively Diagnosed by EUS-FNA: A Case Report and Review of the Literature

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Abstract:

Pancreatic serous cystic neoplasms (SCNs), such as serous cystadenoma (SCA), are generally recognized as benign because malignant counterparts of SCNs have been extremely rare. In clinical practice, pancreatic cystic neoplasms diagnosed as SCNs have been managed by conservative observation, as long as the patients remained asymptomatic. We herein report a case of metachronous ductal adenocarcinoma that was discovered during long-term follow-up of SCN and review the related literature. To our knowledge, this was the first reported case of the local presence of ductal adenocarcinoma adjacent to SCA that was preoperatively diagnosed by endoscopic ultrasound-guided fine-needle aspiration.

Key words: serous cystic neoplasm (SCN), serous cystadenoma (SCA), pancreatic ductal adenocarcinoma (PDAC), endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), diffusion-weighted magnetic resonance image (DWI)

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Introduction

Serous cystic neoplasm (SCN) is relatively uncommon, accounting for only 1% to 2% of all pancreatic tumors (1). It is characterized by cuboidal, glycogen-rich, epithelial cells that produce a watery fluid that is similar to serum. Pathologically, most SCNs are serous cystadenomas (SCAs) and have been recognized as benign neoplasms with almost no malignant potential (2). These tumors are observed conservatively by serial imaging and are not usually recommended for surgical resection.

We herein report a case of metachronous pancreatic ductal adenocarcinoma (PDAC) with an adjacent SCA that was preoperatively detected by endoscopic ultrasonography (EUS) and pathologically diagnosed by EUS-guided fine-needle aspiration (EUS-FNA).

Case Report

A 65-year-old man was incidentally found to have a cystic tumor in the pancreatic head while under observation for a previously diagnosed squamous cell carcinoma of the lung, which was surgically resected at our hospital. The patient's physical symptoms and blood test results, including tumor markers [carcinoembryonic antigen (CEA), 2.0 ng/mL (normal, 0-5 ng/mL); carbohydrate antigen (CA) 19-9, 1.0 U/mL (normal, 0-37 U/mL)], showed no abnormalities. Contrast-enhanced computed tomography (CT) showed a 36 ×34-mm multilobulated and heterogeneous cystic mass in

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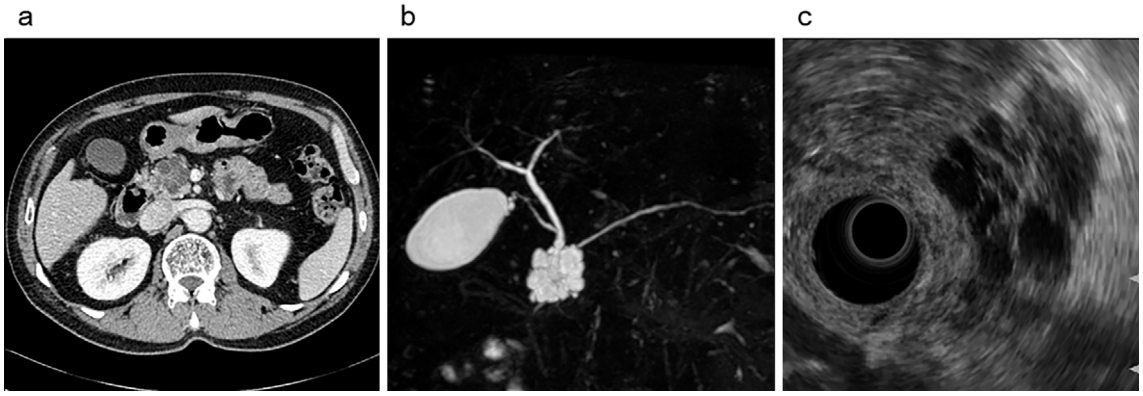

Figure 1. **Images obtained at the initial presentation. a) Contrast-enhanced computed tomography (CT) and (b) magnetic resonance cholangiopancreatography (MRCP) show a 36×34-mm multilobulated and heterogeneous cystic mass in the head of the pancreas. (c) Endoscopic ultrasonography (EUS) shows a honeycomb appearance and a central stellate scar in the cystic mass.**

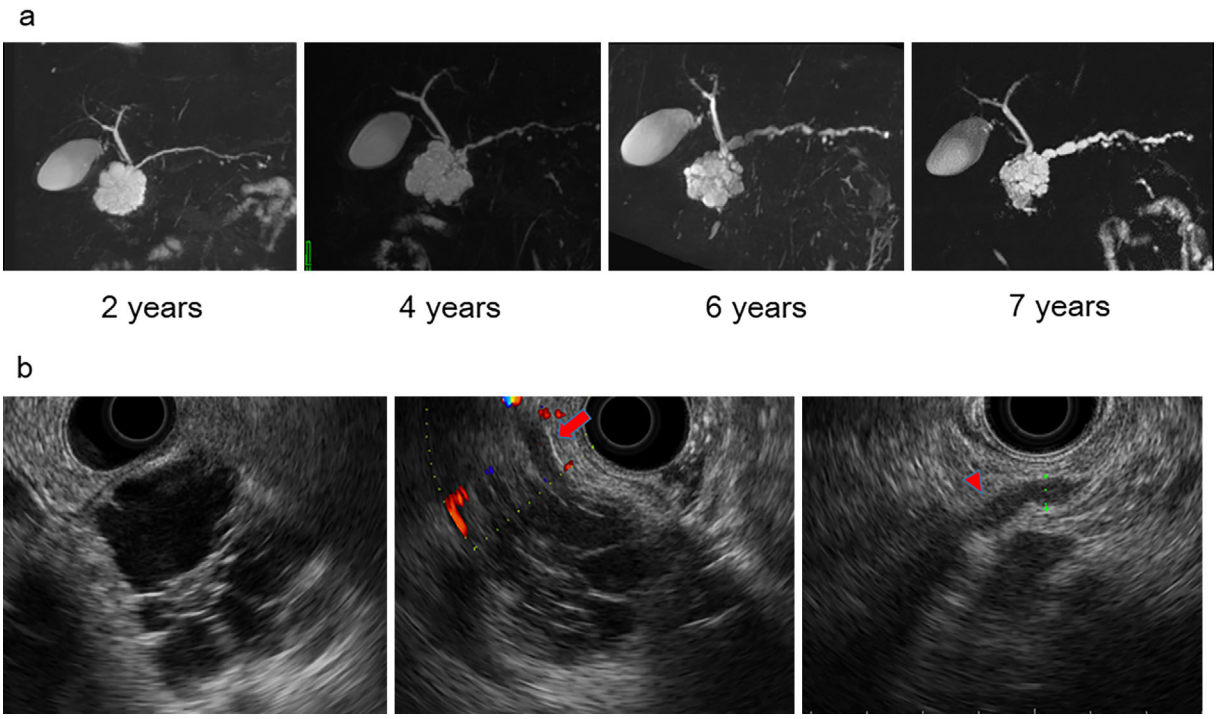

Figure 2. **Serial images during routine checkup. (a) Serial MRCP images after the SCN diagnosis show no remarkable change in the multilobulated cystic mass. After six years, the cystic mass has started obstructing the passage of the main pancreatic duct (MPD), resulting in dilation of the tail side of the MPD. (b) EUS at six years after the initial presentation shows no remarkable change in the characteristics of the cystic lesion (left panel). The common bile duct (CBD) (arrow) is not dilated (middle panel), but the cystic mass is obstructing the MPD, causing subsequent dilation of the tail side of the MPD (arrowhead; right panel).**

the head of the pancreas (Fig. 1a). At this time, magnetic resonance cholangiopancreatography (MRCP) showed that the cystic mass was not causing obstruction of the main pancreatic duct (MPD) or the common biliary duct (CBD) (Fig. 1b). EUS showed a honeycomb appearance and a central stellate scar in the cystic mass (Fig. 1c). These imaging findings strongly indicated mixed-type pancreatic SCN, for which the patient was followed clinically by CT and MRCP every six months, along with routine blood tests (Fig. 2a).

During routine checkups, the multilobulated cystic mass did not seem to have changed remarkably. However, at six years of the initial diagnosis, the MPD became dilated. At this time, the patient's physical symptoms and blood test results, including tumor markers, were still normal. On EUS, the characteristics of the cystic lesion did not seem to have changed, but the cystic mass was now obstructing the MPD

Table 1. Laboratory Findings.

Hematology		Blood chemistry		Tumor markers	
WBC	6,600 /μL	AST	259 U/L	CEA	2.6 ng/mL
RBC	418×10^4 /μL	ALT	381 U/L	CA19-9	0.4 U/mL
Hb	13.0 g/dL	ALP	2,121 U/L		
Plt	28.5×10^4 /μL	γGTP	1,919 U/L		
		T-bil	10.5 mg/dL		
		D-bil	7.0 mg/dL		
		Amylase	84 U/L		
		Lipase	67 U/L		
		Glucose	121 mg/dL		
		TP	7.0 g/dL		
		Alb	3.5 g/dL		
		CRP	3.51 mg/dL		

Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, CRP: C-reactive protein, D-bil: direct bilirubin, γGTP: γ-glutamyltransferase, Plt: platelets, RBC: red blood cells, T-bil: total bilirubin, TP: total protein

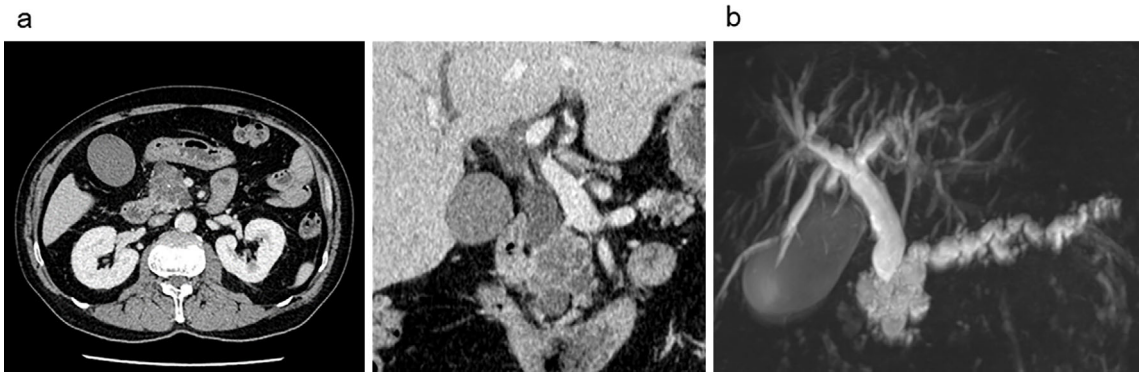

Figure 3. Images obtained eight years after the initial presentation. (a) Contrast-enhanced CT shows a 48×45-mm heterogeneous cystic tumor in the head of the pancreas and biliary obstruction. (b) MRCP shows dilation of both the MPD and CBD.

passage, resulting in the dilation of the upstream MPD (Fig. 2b). The CBD was free from any obstruction. At this time, the plan was further careful observation.

Two years later, the patient noticed skin jaundice and visited our hospital before his next routine checkup, at which point he was admitted for a further examination. Although the hepatic transaminase and biliary enzyme levels were elevated, the tumor marker levels remained normal (CEA, 2.6 ng/mL; CA19-9, 0.4 U/mL) (Table 1). Contrast-enhanced CT at this time showed a 48×45-mm heterogeneous cystic tumor in the head of the pancreas, with biliary obstruction (Fig. 3a). MRCP showed dilation of the MPD and CBD (Fig. 3b). Based on these findings, part of the SCN seemed to have caused the obstruction of the CBD and MPD. However, careful EUS identified a neighboring hypoechoic solid tumor that measured 16 mm in diameter as the direct cause of CBD obstruction (Fig. 4a). EUS-FNA was performed to obtain tissue samples from the solid tumor, which was found to contain adenocarcinoma on a pathological examination (Fig. 4b). Based on these results, the diagnosis was PDAC combined with SCN.

After endoscopic biliary drainage (Fig. 4c), the patient underwent subtotal stomach-preserving pancreaticoduodenectomy. Similar to the preoperative images, the resected specimen showed a lobulated cystic tumor replacing the head of the pancreas (Fig. 5a). The 22×15-mm solid tumor that was adjacent to the cystic tumor was confirmed to obstruct the CBD. A histological examination showed combined PDAC and SCA without metastasis (Fig. 5b).

Discussion

SCN of the pancreas was initially described by Compagno and Hodgkinson in 1978 (3, 4) as having a sponge-like appearance, comprising multiple microcysts lined by flattened or cuboidal glycogen-rich cells (2). In terms of the microscopic and gross morphology, SCNs are currently classified as microcystic (classic type); microcystic with a macrocystic component (mixed type); macrocystic, which is subclassified into the multilocular and unilocular types; and solid (5). Most SCNs are recognized as benign cystadenomas. Therefore, the current management of SCNs is conser-

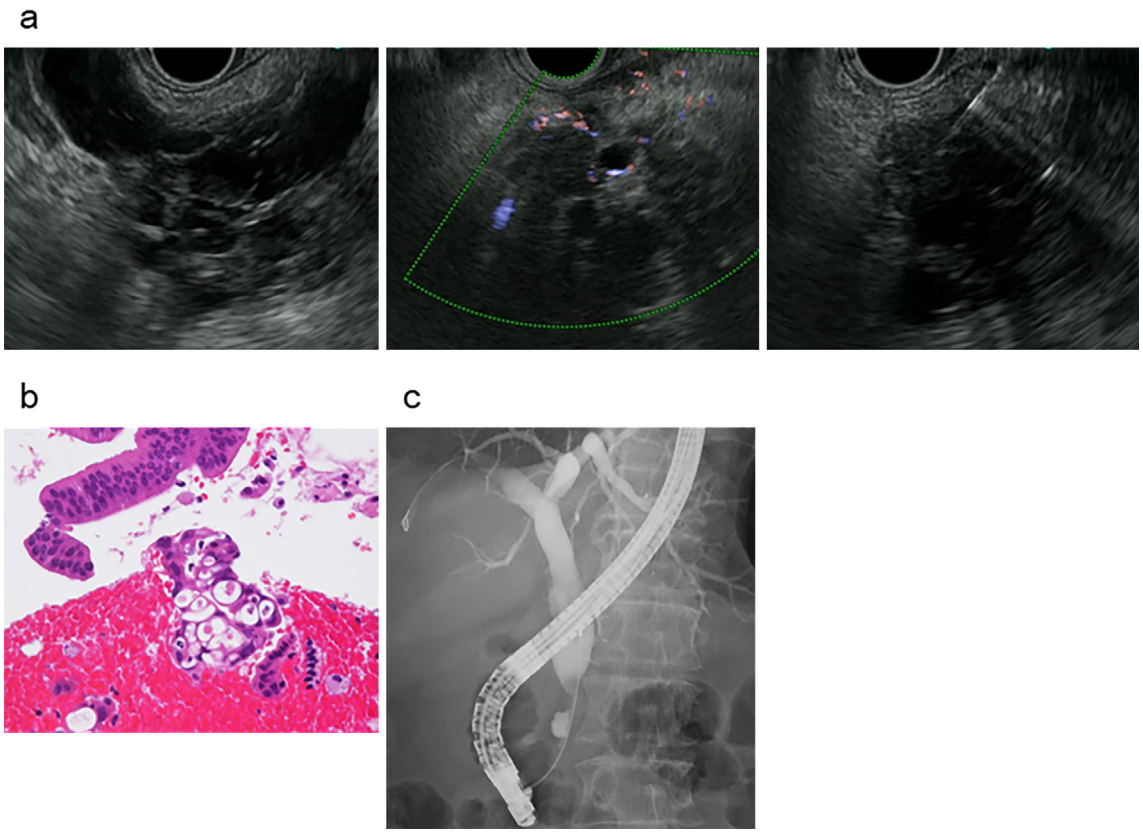

Figure 4. **Images obtained eight years after the initial presentation. (a) EUS shows part of the SCN causing CBD obstruction and subsequent upstream dilation (left panel). Careful EUS shows a neighboring solid tumor as the direct cause of CBD obstruction (middle panel). EUS-guided fine-needle aspiration (EUS-FNA) is performed to obtain tissue samples from the solid lesion (right panel). (b) Pathological images of the pancreatic tissue specimens obtained by EUS-FNA show the presence of adenocarcinoma (Hematoxylin and Eosin staining; original magnification, ×400). (c) Endoscopic retrograde cholangiography shows distal obstruction of the CBD with dilation of the hilar BD.**

vative observation, as long as the patient is asymptomatic.

In this report, we presented a case of coexistence of PDAC and SCA. The questions raised in this case were 1) Was the diagnosis serous cystadenocarcinoma? and 2) Did the adenocarcinoma arise from the preexisting SCA, or was it originally independent of the cystadenoma? A serous cystadenocarcinoma is defined as a malignant counterpart of SCNs and is extremely rare. Malignant SCN was first reported as the imaging finding of synchronous tumors in the liver (6). The first histologically proven case of serous cystadenocarcinoma showed direct invasion of the spleen and metastases to the stomach and liver (7). Subsequently, more than 20 cases of malignant SCNs have been reported.

However, as shown in the 2010 World Health Organization (WHO) classification and in other clinical reports, serous cystadenocarcinoma is indistinguishable from its benign counterparts. The benign and malignant variants appear identical histologically, with gross or microscopic evidence of distant metastases the only distinguishing feature.

True malignant formation in the form of adenocarcinoma is an extremely uncommon phenomenon in SCNs. Reid et al. investigated the clinicopathologic characteristics of 193 SCNs and reviewed the related literature; they stated that SCNs, including the so-called serous cystadenocarcinoma, should not be classified as malignant unless there is clear-cut histologic evidence of malignancy or validated distant metastasis (8). Intriguingly, they mentioned that the simultaneous occurrence of SCNs, even in the liver, might represent synchronous disease rather than true metastases. Therefore, based on the above-mentioned current classification and previous reports, this case did not qualify as serous cystadenocarcinoma because of the lack of distant metastases.

Regarding the second question, a review of available literature revealed a report by Zhu et al. concerning an extremely rare case of histologically proven 3-cm malignant serous neoplasm, specifically carcinoma ex microcystic adenoma, with metastasis to regional lymph nodes (9); this was histologically reassessed and reported in another study as having some features of serous neoplasm (8). For that reported case, the final diagnosis was carcinoma that arose from the preexisting SCA, based on the following pathological evidence: 1) the carcinoma components were found within the typical SCA; 2) the areas of transition between the benign and malignant components were identified microscopically; and 3) all areas shared similar immunohistochemical profiles.

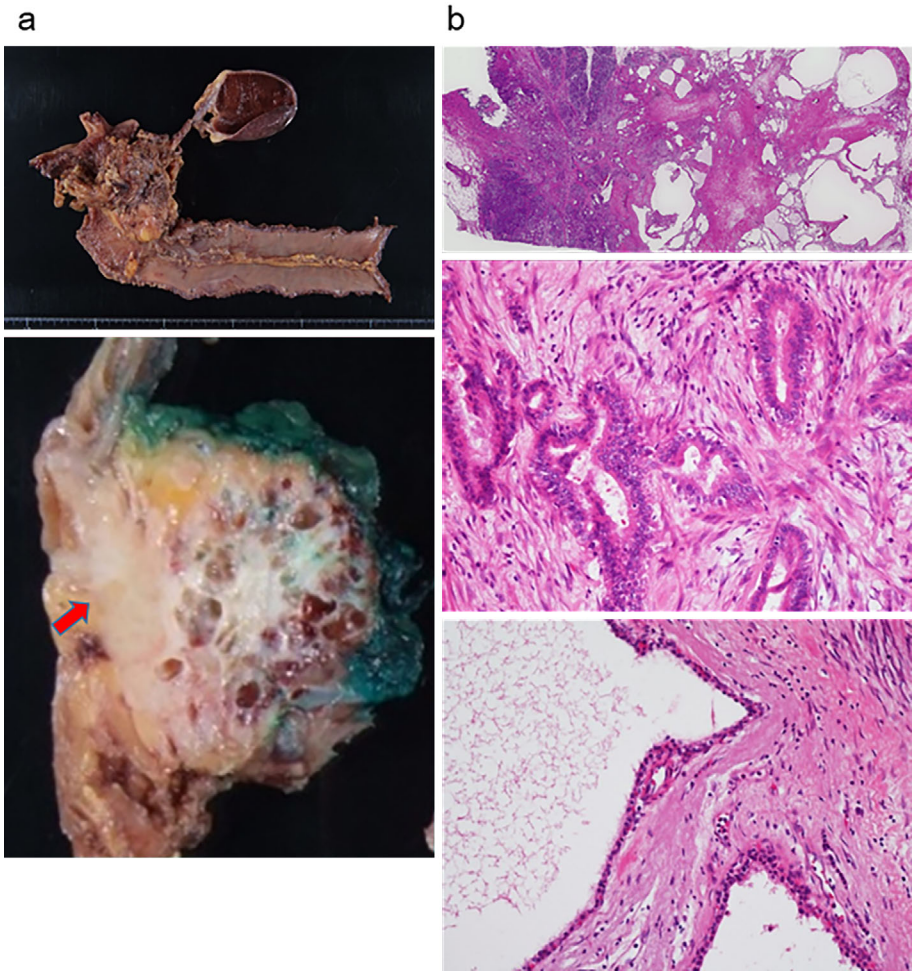

Figure 5. Pathological images of the resected specimen. (a) Grossly, the specimen resected by subtotal stomach-preserving pancreaticoduodenectomy shows a lobulated cystic tumor replacing the head of the pancreas and confirms the presence of a 22×15-mm solid tumor (arrow) adjacent to the cystic tumor. (b) A whole-mount sample stained with Hematoxylin and Eosin staining (upper panel) shows ductal adenocarcinoma in the solid tumor (PDAC) (middle panel; original magnification, ×200) that is adjacent to a serous cystadenoma (SCA) (lower panel; original magnification, ×200), with a relatively clear border.

Applying these principles in our case, although invasive ductal adenocarcinoma was observed adjacent to the SCA, the border was relatively clear, and there was no evidence of carcinoma within the area of the SCA. In addition, the high-grade intraepithelial neoplasia of the pancreatic duct was detected in the area of the PDAC, which indicated it to be the origin of ductal neoplasm. Furthermore, the immunohistochemical profiles differed between the SCA and PDAC. As shown in Fig. 6, unlike the SCA, the PDAC did not stain positive for inhibin or mucin 6 (MUC6), which are well-known markers of SCN (10, 11). Genetic investigations would be useful for further verifying the independence of the PDAC component. Von Hippel-Lindau (VHL)-associated tumors are known variants of SCNs (12); accordingly, an analysis of the *VHL* mutation might provide clues to the genetic concordance between SCA and PDAC. In addition, an analysis of the *KRAS* mutation might be effective, as unlike PDAC, SCN rarely has a *KRAS* mutation (13, 14). However, genetic verification has yet to be performed in the present case because of the lack of the patient's consent.

The independent coexistence of ductal carcinoma and benign SCN is very uncommon. To our knowledge, only seven case reports have described the coexistence of ductal carcinoma and SCA (15-21). These previous reports and the current case are summarized in Table 2. In total, there were 9 cases (5 men and 4 women) with a mean age of 72 years old. The symptoms that prompted the hospital visit were epigastric pain (33%, 3/9), jaundice (33%, 3/9), and weight loss (22%, 2/9). Pancreatic SCA (n=9) had a mean size of 48 mm and was located in the pancreatic head in 5 patients (55%), in the body in 3 patients (33%), and in the tail in 1 patient (11%). Pancreatic ductal carcinoma (n=9) had a mean size of 25 mm and was located in the head in 5 patients (55%) and in the body and tail in 2 patients (22%). Only 3 cases (33%, 3/9) had ductal carcinoma adjacent to the SCA. Three cases (33%, 3/9) showed upper CBD dilation with obstructive jaundice. Most cases (83%, 5/6) showed MPD dilation caused by tumor obstruction. In 6

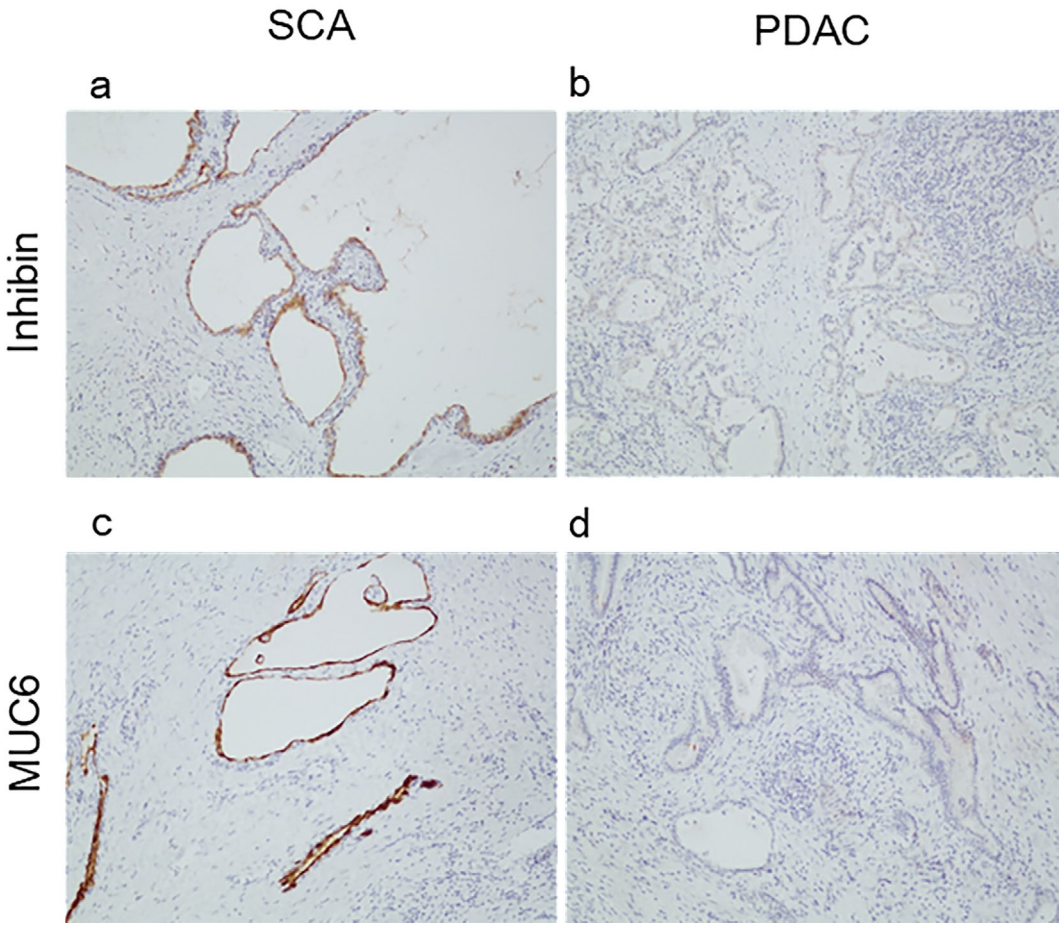

Figure 6. **Immunohistochemical staining of the pathological images. Inhibin is positive in the SCA sample (a) (original magnification, ×100) but not in the PDAC sample (b) (original magnification, ×100). MUC6 is positive in the SCA sample (c) (original magnification, ×100) but not in the PDAC sample (d) (original magnification, ×100). MUC6: mucin 6, PDAC: pancreatic ductal adenocarcinoma, SCA: serous cystadenoma**

cases (66%, 6/9), ductal carcinoma and SCN were coincidently detected. Our case was the only one in which EUS-FNA was performed to obtain a tissue sample from the solid lesion, which resulted in the preoperative pathological diagnosis of PDAC. In 8 cases (88%, 8/9), surgical resection was performed. According to our review of the literature, our case was unique for the following reasons: 1) the presence of adjacent tumors, which were more difficult to detect than tumors located farther apart; 2) the longest duration (i.e. 8 years) of follow-up of SCN prior to detecting PDAC; and 3) the first case (to our knowledge) in which the existence of PDAC was detected preoperatively and diagnosed pathologically by EUS-FNA.

EUS has become an indispensable tool for the diagnosis of pancreatic diseases. Compared with the other standard imaging modalities, including CT and magnetic resonance imaging (MRI), EUS can provide excellent images of pancreatic diseases. In addition to its ability to scan target organ, EUS has the strong advantage of being able to make a preoperative pathologic diagnosis of the target disease using FNA, which can obtain a significant amount of tissue sample. In the current case, a further review of the diffusion-weighted MRI [diffusion-weighted imaging (DWI)] findings showed a focal hyperintense signal in the PDAC lesion six months before the obstructive jaundice occurred (Fig. 7). DWI is a technique based on the Brownian motion of water molecules in tissues (22) and was indicated by previous studies to be useful for assessing pancreatic tumors (23-25). In hindsight, we would like to emphasize the importance of paying attention to the DWI findings in addition to the findings on conventional MRI sequences during routine checkup of SCN.

According to several reports that analyzed the clinicopathological characteristic of SCNs (5, 26-29), only 1% to 7% of patients had obstructive jaundice due to CBD obstruction, whereas 27% to 50% presented with MPD obstruction or distortion. These features were observed more frequently in the coexistent group (CBD dilation, 33%, 3/9; MPD dilation, 83%, 5/6) than the previous reviews of SCN and might provide clues for how to improve the careful investigation of uncommon SCNs.

In conclusion, we described a case of metachronous PDAC with adjacent SCA that was preoperatively diagnosed by EUS-FNA. Our experience strongly supports the possibil-

Table 2. Reported Cases of the Coexistence of Serous Cystadenoma and Ductal Carcinoma in the Pancreas.

	Ref. No.	Sex	Age	Symptom	SCA Size Location	DC Size Location	Distance between SCA and DC	CBD dilation	MPD dilation	Time to DC diagnosis after SCA	Preoperative pathological diagnosis of DC	Treatment	Pathology	TNM
1	(15)	M	62	Epigastric pain B.W. loss	40 mm Pb	n.d Ph	Distant	No	n.d	Coincident	No	TP	Adeno.ca	-
2	(15)	F	59	Epigastric pain	70 mm Pb	30 mm Pt	Distant	No	n.d	Coincident	No	TP	Adeno.ca	T3N0M0
3	(16)	F	79	Epigastric pain B.W. loss	40 mm Ph	n.d Pt	Distant	No	No	Coincident	Yes (FNA)	none	Adeno.ca	TXNXM1
4	(17)	M	72	Jaundice	80 mm Ph	30 mm Ph	Adjacent	Yes	Yes	3 years	No	PD	Adeno.ca.	T3N1M0
5	(18)	M	72	None	32 mm Ph	15 mm Pb	Distant	No	Yes	Coincident	No	SSPPD	Adeno.ca.	T1N1M0
6	(19)	F	79	Jaundice	30 mm Ph	30 mm Ph	Adjacent	Yes	n.d	Coincident	No	PD	Adeno.ca.	T3N0M0
7	(20)	M	70	None	52 mm Pb	37 mm Ph	Distant	No	Yes	Coincident	No	PD	Adenosqua.ca.	T3N1M0
8	(21)	F	65	None	45 mm Pt	12 mm Pb	Distant	No	Yes	2 years	No	DP	Adeno.ca.	T1N0M0
9	Our case	M	73	Jaundice	45 mm Ph	21 mm Ph	Adjacent	Yes	Yes	8 Years	Yes (EUS-FNA)	SSPPD	Adeno.ca	T3N0M0

Adeno.ca: adenocarcinoma, Adenosqua.ca, adenosquamous carcinoma, CBD: common bile duct, DC: ductal carcinoma, EUS: endoscopic ultrasound, FNA: find needle aspiration, MPD: main pancreatic duct, n.d: no data, Pb: pancreatic body, PD: pancreaticoduodenectomy, Ph: pancreatic head, Pt: pancreatic tail, SCA: serous cystadenoma, SSPPD: subtotal stomach-preserving pancreaticoduodenectomy, TP: total pancreatectomy

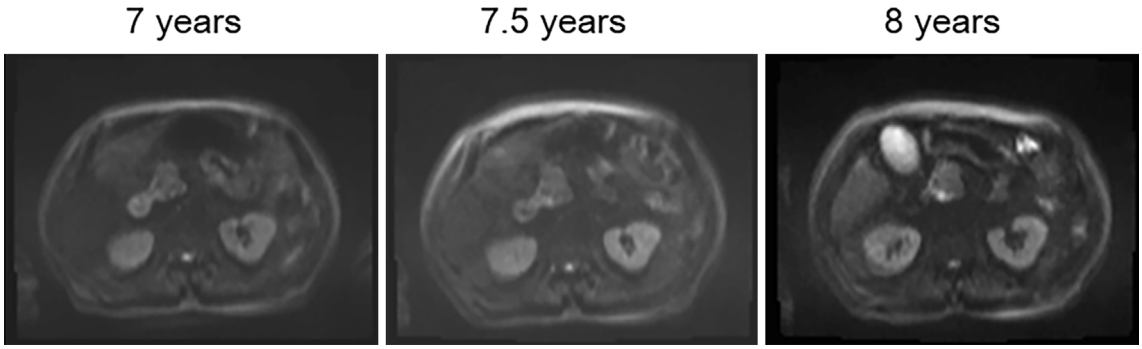

Figure 7. Serial images of diffusion-weighted MRI during routine checkup. At seven years after the initial presentation, before the occurrence of obstructive jaundice, the image shows no intense signal (left panel). Six months later, a focal hyperintense signal is seen in the pancreatic head (middle panel). After another six months, at the time of the occurrence of obstructive jaundice, the focal signal is more obvious (right panel).

ity of adjacent PDAC in patients with SCNs and the utility of DWI in detecting this possibility during routine follow-up of SCN. Obstruction of the CBD or MPD secondary to a neighboring SCN might be a significant sign of a coexistent PDAC. Although SCNs are generally benign tumors, more careful and unbiased EUS examinations are important for detecting metachronous PDACs.

The authors state that they have no Conflict of Interest (COI).

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