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

Michihiro Yoshida, Itaru Naitoh, Kazuki Hayashi, Naruomi Jinno, Makoto Natsume, Yasuki Hori, Akihisa Kato, Kenta Kachi, Go Asano, Yoichi Matsuo, Satoru Takahashi and Hiromi Kataoka

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)

(Intern Med Advance Publication) (DOI: 10.2169/internalmedicine.3912-19)

Introduction
Serous cystic neoplasm (SCN) is relatively uncommon, accounting for only 1% to 2% of all pancreatic tumors (1). It is characterized by cuboidal, glycoprotein-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 (CEA, 2.0 ng/mL [normal, 0-5 ng/mL]; CA 19-9, 1.0 U/mL [normal, 0-37 U/mL]), showed no abnormalities. Contrast-enhanced computed tomography (CT) showed a 36x34-mm multilobulated and heterogeneous cystic mass in 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.

Figure 1. Images obtained at the initial presentation. a) Contrast-enhanced computed tomography (CT) and (b) magnetic resonance cholangiopancreatography (MRCP) show a 36x34-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).
Table 1. Laboratory Findings.

| Hematology | Blood chemistry | Tumor markers |
|------------|-----------------|---------------|
| WBC 6,600 /μL | AST 259 U/L | CEA 2.6 ng/mL |
| RBC 418x10^6 /μL | ALT 381 U/L | CA19-9 0.4 U/mL |
| Hb 13.0 g/dL | ALP 2,121 U/L | |
| Plt 28.5x10^4 /μL | γGT 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, γGT: γ-glutamyltransferase, Plt: platelets, RBC: red blood cells, T-bil: total bilirubin, TP: total protein

**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 consen-
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 SCA. 

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 above-mentioned current classification and previous reports, this case did not qualify as serous cystadenocarcinoma because of the lack of distant metastases.

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; original magnification,×400). (c) Endoscopic retrograde cholangiography shows distal obstruction of the CBD with dilation of the hilar BD.
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%), 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
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 possibilit-

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

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

| Ref. No. | Year | 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        | 1990 | M   | 62  | Epigastric pain | 40 mm    | Pb       | n.d     | Ph       | Distant                   | No           | n.d         | Coincident                       | No                                | TP        | Adeno.ca  | -   |
| 2        | 1990 | F   | 59  | Epigastric pain | 70 mm    | Pb       | 30 mm   | Pt       | Distant                   | No           | n.d         | Coincident                       | No                                | TP        | Adeno.ca  | T3N0M0|
| 3        | 1991 | F   | 79  | Epigastric pain | 40 mm    | Ph       | n.d     | Pt       | Distant                   | No           | No          | Coincident                       | Yes (FNA)                          | none      | Adeno.ca  | TXXM1|
| 4        | 1994 | M   | 72  | Jaundice      | 80 mm    | Ph       | 30 mm   | Pt       | Adjacent                  | Yes          | Yes         | 3 years                         | No                                | PD        | Adeno.ca  | T3N1M0|
| 5        | 2008 | M   | 72  | None         | 32 mm    | Ph       | 15 mm   | Ph       | Distant                   | No           | Yes         | Coincident                       | No                                | SSPPD     | Adeno.ca  | T1N1M0|
| 6        | 2008 | F   | 79  | Jaundice      | 30 mm    | Ph       | 30 mm   | Ph       | Adjacent                  | Yes          | n.d         | Coincident                       | No                                | PD        | Adeno.ca  | T3N0M0|
| 7        | 2012 | M   | 70  | None         | 52 mm    | Pb       | 37 mm   | Ph       | Distant                   | No           | Yes         | Coincident                       | No                                | PD        | Adenosq. | T3N1M0|
| 8        | 2013 | F   | 65  | None         | 45 mm    | Pt       | 12 mm   | Ph       | Distant                   | No           | Yes         | 2 years                         | No                                | DP        | Adeno.ca  | T1N0M0|
| 9        |      | M   | 73  | Jaundice      | 45 mm    | Ph       | 21 mm   | Ph       | Adjacent                  | Yes          | Yes         | 8 Years                         | Yes                                | SSPPD     | Adeno.ca  | T3N0M0|
|          |      |     |     |           |          |          |         |          |                           |              |            |                                 | (EUS-FNA)                                         |

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

The utility 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.
**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).

**Acknowledgement**

The authors thank Dr. Kenji Notohara (Department of Anatomic Pathology, Kurashiki Central Hospital, Japan) for his pathological diagnostic input.

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